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CONTENTS

ERRATA

Volume 28, Number 2, April, 1941

Page 186: In the third line from the bottom of the page replace "reduce" by "oxidize."

Volume 30, Number 3, June, 1942

Page 408: The sign before the final term in equation 14 should be plus instead of minus.

In the equation immediately preceding equation 14, the numerical coefficient of the final term should be 0.868 instead of 0.858.

THE ULTRAVIOLET ABSORPTION SPECTRA OF AROMATIC HYDROCARBONS[1]

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The ultraviolet absorption spectrum is of considerable value in the determination of the structure of an aromatic hydrocarbon. It has been used frequently for this purpose in synthetic organic chemistry, as well as in studies of natural products and of other substances of biological importance, such as the carcinogenic hydrocarbons.

The influence of various structural factors on the absorption spectra of aromatic hydrocarbons is discussed, particularly with respect to changes produced in the spectra by the introduction of alkyl substituents, alicyclic groups, and alkene and cycloalkene groups. References to the absorption spectra of about three hundred and seventy hydrocarbons are collected in tables.

I. INTRODUCTION

This article is concerned primarily with an assessment of the possibilities and limitations of ultraviolet spectrophotometry as a method of characterizing aromatic hydrocarbons.

Although the mechanism of the absorption of ultraviolet light by organic molecules is still understood very imperfectly, much empirical knowledge has been accumulated, which has proved of considerable value in the elucidation of the structure of organic compounds (69, 71, 204). This is true particularly of substances which contain a simple chromophore, such as a carbonyl group, a conjugated diene, or an α,β-unsaturated carbonyl system, where the spectra are without fine structure and the chromophoric system can be identified by the position and intensity of the maximum, or occasionally two maxima, present.

The spectra of certain types of aromatic hydrocarbons, particularly those which contain several condensed benzene rings, may be exceedingly complex: e.g., the spectrum of 1,2-benzanthracene (I) (see figure 1). A dozen or more maxima may be present in the middle ultraviolet region between 2300 and 3900 Å. These maxima are usually attributed to several levels of vibrational activation associated with one or two primary electronic activation states, but
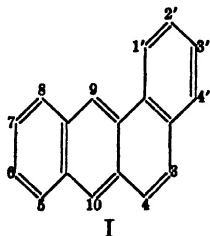
I

1,2-Benzanthracene

details of the absorption process are still obscure.   The absorption spectra of a
great many hydrocarbons of this type have been measured; the spectra are
characteristic of the particular system of fused aromatic rings involved and pro-
vide a reliable method for the identification of that ring system.   Spectra of
such a complex type cannot be described adequately by a list of the wave length
and intensity of the maxima and minima, and similarities and differences be-
tween the spectra of two compounds can be discerned most readily if the two
spectra are plotted on the same graph (figures 7 and 8).   References to the
spectra of unsubstituted hydrocarbons of this type are included in table 1.
Alkyl, alicyclic, and alkene derivatives of these and other hydrocarbons are
discussed elsewhere in this article.
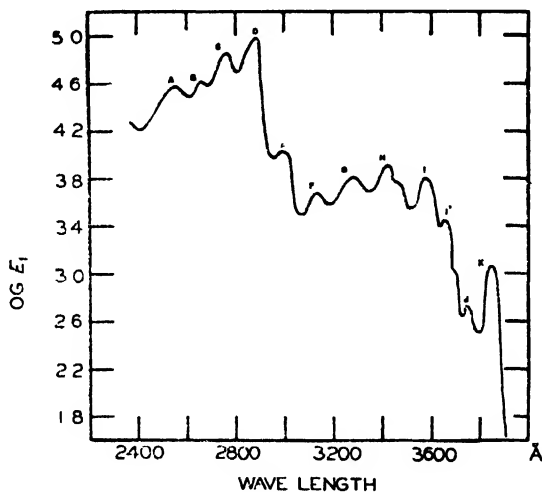
Fig. 1. Ultraviolet absorption spectrum of 1,2-benzanthracene in ethanol as solvent (132)

Polynuclear aromatic hydrocarbons in which phenyl groups are attached
together through a single carbon-to-carbon linkage, as in diphenyl (LIIa), or
in which the phenyl groups are linked through a chain of conjugated double
bonds as in stilbene and 1,4-diphenylbutadiene, usually possess·spectra of a
much simpler type containing seldom more than three maxima (figure 2).   If
the phenyl groups are separated from one another by one or more methylene
groups, there is negligible interaction between them, and aromatic systems in
the same molecule, which are so separated, contribute additively to the total
light absorption of the molecule.   This is illustrated in figure 3, where the spectra
of dibenzyl (II), diphenylmethane (III), and triphenylmethane (IV) are com-
pared with that of a typical alkyl derivative of benzene.

II
Dibenzyl

III
Diphenylmethane

IV
Triphenylmethane
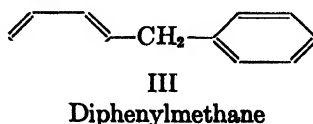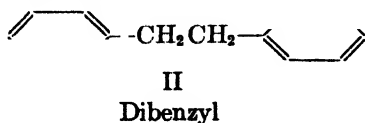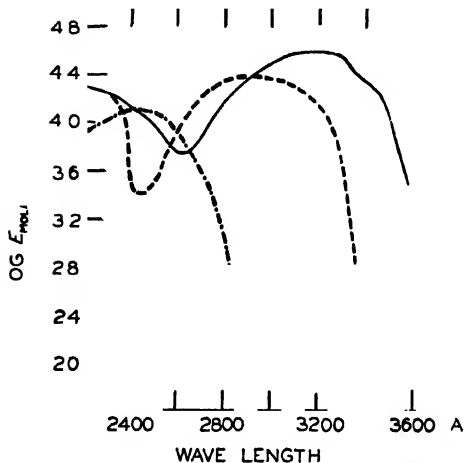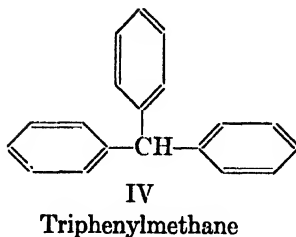
FIG. 2. Ultraviolet absorption spectra. ——, 1,4-diphenyl-1,3-butadiene in ethanol as solvent (92); ----, *trans*-stilbene in ethanol as solvent (7); —·—·, diphenyl in methanol as solvent (154).

FIG. 3a. Ultraviolet absorption spectra. ——, triphenylmethane in ethanol as solvent (217); ----, diphenylmethane in ethanol as solvent (217).

FIG. 3b. Ultraviolet absorption spectra. ——, dibenzyl in methanol as solvent (154); ----, ethylbenzene in ethanol as solvent (97).

TABLE 1

References to the absorption spectra of unsubstituted aromatic hydrocarbons

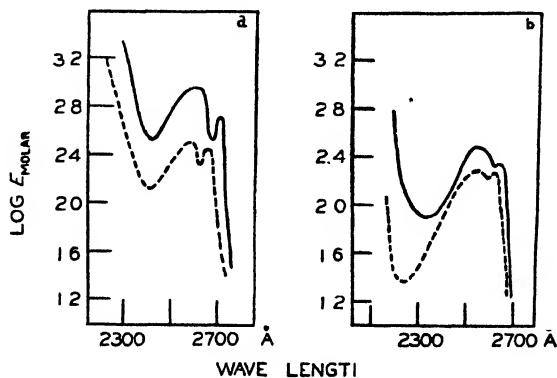| COMPOUND	RING INDEX* NUMBER	REFERENCES
A. One benzene ring:		
C_6D_6 Hexadeuterobenzene		(243[b])
C_6H_6 Benzene....	215	(10, 12[e], 18, 25, 29, 30, 35[bd], 36, 46, 59, 61, 71, 81, 94, 95, 99, 103, 104, 109, 110[de], 111, 112, 113, 115, 117, 121, 126, 138, 139, 140, 142, 144, 147, 149, 150, 152, 153, 157, 160, 161, 164, 166, 169, 170[f], 172, 173, 180, 184[bd], 189, 190, 191, 192, 197, 207, 224, 235, 244[b], 249, 250, 259, 260)
B Two benzene rings:		
$C_{10}H_8$ Naphthalene	1053	(9, 14[e], 29, 46, 55, 62, 81, 93, 103, 104, 109, 111, 115, 117, 150[e], 152[e], 157, 164, 169, 193, 202, 234[j], 248, 249, 250)
$C_{12}H_8$ Biphenylene	1271	(34)
$C_{12}H_{10}$ Diphenyl		(1, 18, 19, 37[b], 67, 71, 94, 95, 105, 111, 114, 115, 135, 154, 164, 186, 188, 193, 194, 197, 198, 204, 205, 207, 234, 247, 249, 250, 254)
$C_{13}H_{10}$ Fluorene†	1775	(9, 26, 67, 131, 154, 170, 174, 207, 217, 234[j], 249)
C. Three benzene rings:		
$C_{14}H_{10}$ Anthracene	2029	(14[e], 17[e], 25, 29, 33, 38, 41, 44, 46, 62, 66, 67, 90, 103, 104, 108, 109, 126, 148, 152, 155, 164, 169, 188, 202, 228, 234[j], 242, 246, 253)
$C_{14}H_{10}$ Phenanthrene	2030	(8, 9, 14[e], 33, 38, 41, 45, 46, 50, 55, 67, 81, 98, 109, 112, 130 152, 164, 169, 188, 202, 228 234[j], 249)
$C_{16}H_{10}$ Fluoranthrene	2568	(234[e])
$C_{16}H_{12}$ 1-Phenylnaphthalene.		(131)
$C_{16}H_{12}$ 2-Phenylnaphthalene.		(85, 131, 135)
$C_{17}H_{12}$ 1,2-Benzfluorene	2558	(14[e], 131, 170)
$C_{17}H_{12}$ 3,4-Benzfluorene....	2560	(131, 170)
$C_{18}H_{14}$ o-Diphenylbenzene.		(198)
$C_{18}H_{14}$ m-Diphenylbenzene (m-terphenyl).....		(94, 95, 198)
$C_{18}H_{14}$ p-Diphenylbenzene (p-terphenyl)......		(94, 95, 198, 234)
$C_{19}H_{14}$ 9-Phenylfluorene.		(217)
$C_{19}H_{15}$ Triphenylmethyl (cation).............		(4, 90)
(anion).		(5, 90)
(free radical)		(5, 31, 90)
D. Four benzene rings:		
$C_{16}H_{10}$ Pyrene‡....	2813	(14[e], 47, 91, 105, 169, 193, 202, 203, 234[j], 246, 249, 250)
$C_{17}H_{12}$ 7-Benzanthrene.......	2812	(51)
$C_{18}H_{12}$ 1,2-Benzanthracene.............	2805	(14[e], 33, 44, 132, 169, 227)
$C_{18}H_{12}$ Chrysene...........................	2806	(14[e], 28, 50, 55, 169, 227, 234[j], 249, 250)

TABLE 1—*Continued*

COMPOUND	RING INDEX° NUMBER	REFERENCES

D. Four benzene rings:—Continued

$C_{18}H_{12}$	3,4-Benzphenanthrene.............. ...	2807	(170)
$C_{18}H_{12}$	2,3-Benzanthracene (naphthacene)....	2804	(14°, 46, 74ᵃ, 106ʰ, 201, 203, 234ʲ)
$C_{18}H_{12}$	Triphenylene.......	2808	(14°, 55, 174)
$C_{20}H_{14}$	9-Phenylanthracene.................		(33)
$C_{20}H_{14}$	1,1'-Dinaphthyl....................		(2, 24, 188)
$C_{20}H_{14}$	2,2'-Dinaphthyl....		(2)
$C_{21}H_{14}$	1',2'-Naphtho-2,3-fluorene...........	3157	(64, 170)
$C_{21}H_{14}$	2',1'-Naphtho-1,2-fluorene.........	3161	(169)
$C_{21}H_{14}$	1,2,3,4-Dibenzfluorene..	3162	(174)
$C_{21}H_{14}$	1,2,5,6-Dibenzfluorene	3165	(170)
$C_{24}H_{16}$	Biacenaphthylidene (biacene, heptacyclene).................	3673	(15)
$C_{24}H_{18}$	4,4'-Diphenyldiphenyl (*p*-quaterphenyl).........		(1, 94, 95)
$C_{24}H_{18}$	1,3,5-Triphenylbenzene.............. .		(234)
$C_{25}H_{20}$	Tetraphenylmethane..............		(94)

E. Five benzene rings:

$C_{20}H_{12}$	3,4-Benzpyrene‡....	3382	(11, 14°, 47, 137, 169, 171)
$C_{20}H_{12}$	Perylene	3384	(14°, 45, 68ᵃ, 105, 106, 112, 188, 195ʰ, 196, 203, 234°)
$C_{22}H_{14}$	2,3,6,7-Dibenzanthracene (pentacene).	3362	(46)
$C_{22}H_{14}$	1,2,3,4-Dibenzanthracene	3367	(42, 44, 50, 55)
$C_{22}H_{14}$	1,2,5,6-Dibenzanthracene	3369	(14°, 42, 50, 73, 137, 157, 159, 169, 234ᵏ)
$C_{22}H_{14}$	1,2,6,7-Dibenzanthracene (2',3'-naphtho-2,3-phenanthrene)	3363	(43, 44, 50, 55)
$C_{22}H_{14}$	1,2,7,8-Dibenzanthracene	3368	(51)
$C_{22}H_{14}$	2,3,6,7-Dibenzphenanthrene (2',3'-naphtho-1,2-anthracene) (pentaphene)	3364	(44, 46, 50, 53, 54)
$C_{22}H_{14}$	1,2,7,8-Dibenzphenanthrene (picene)..	3370	(169, 226, 227)
$C_{22}H_{14}$	1,2,6,7-Dibenzphenanthrene (2',3'-naphtho-1,2-phenanthrene)...	3365	(43, 44, 50, 55)
$C_{22}H_{14}$	2,3,5,6-Dibenzphenanthrene (2',3'-naphtho-3,4-phenanthrene)...	3366	(56)
$C_{26}H_{18}$	9,10-Diphenylanthracene.............		(105, 135, 202)
$C_{30}H_{22}$	*p*-Quinquephenyl...		(94)

F. Six benzene rings:

$C_{22}H_{12}$	Anthanthrene........	3659	(50)
$C_{22}H_{12}$	1,12-Benzperylene....	3661	(45)
$C_{24}H_{14}$	1,2,3,4-Dibenzpyrene‡..............	3656	(47)
$C_{24}H_{14}$	3,4,8,9-Dibenzpyrene‡	3654	(47)
$C_{24}H_{14}$	3,4,9,10-Dibenzpyrene‡................	3655	(47)
$C_{24}H_{14}$	2',3'-Naphtho-3,4-pyrene‡....	3652	(47)
$C_{24}H_{18}$	2,2'-Diphenyldiphenyl (2,2"-diphenylyldiphenyl)		(1)
$C_{26}H_{16}$	2',3'-Phenanthro-2,3-phenanthrene....	3644	(50)
$C_{26}H_{16}$	2',1'-Anthraceno-1,2-anthracene.......	3645	(44, 50, 57)
$C_{26}H_{16}$	2',3'-Phenanthro-1,2-anthracene (3,4-benzpentaphene)....................	3646	(53)
$C_{26}H_{16}$	1',2'-Anthraceno-1,2-anthracene.......	3647	(57)
$C_{26}H_{16}$	1,2,3,4,5,6-Tribenzanthracene.........	3648	(50)
$C_{28}H_{18}$	9,9'-Dianthryl.....................		(17ᵉ, 44, 135)

TABLE 1—*Concluded*

COMPOUND		RING INDEX[*] NUMBER	REFERENCES
F. Six benzene rings:—Continued			
$C_{26}H_{18}$	9,9'-Diphenanthryl....................		(116)
$C_{29}H_{18}$	1'-Phenyl-2',3'-indeno-3,4-pyrene......		(47)
$C_{30}H_{20}$	9,10-Diphenylnaphthacene............		(75[a])
$C_{30}H_{20}$	9,11-Diphenylnaphthacene............		(75[a])
$C_{30}H_{20}$	2,8-Diphenylchrysene..................		(168)
$C_{36}H_{26}$	*p*-Sexiphenyl		(94)
G. Seven benzene rings:			
$C_{24}H_{12}$	Coronene.............................	3842	(187)
$C_{28}H_{16}$	2,3,10,11-Dibenzperylene.............	3834	(45, 105)
$C_{30}H_{18}$	3,4,9,10-Dibenzpentaphene		(53)
$C_{34}H_{22}$	9,10-Di (1-naphthyl)anthracene...... .		(52, 135)
$C_{36}H_{18}$	Decacyclene	3954	(15)
H. Eight benzene rings:			
$C_{42}H_{28}$	9,10,11,12-Tetraphenylnaphthacene (rubrene).........		(76[a], 114)
$C_{48}H_{28}$	Fluorocyclene..	3971	(15, 102, 252)
I. Nine benzene rings:			
$C_{54}H_{38}$	*m*-Noviphenyl......		(94)
J. Ten benzene rings:			
$C_{54}H_{36}$	9,11-Diphenyl-10,12-bisdiphenylnaph- thacene........		(77[a])
$C_{60}H_{42}$	*m*-Deciphenyl..........		(94)
K. Eleven benzene rings:			
$C_{66}N_{46}$	*m*-Undeciphenyl		(94)
L. Twelve benzene rings:			
$C_{66}H_{44}$	2,6,10,12-Tetraphenyl-9,11-bisdi- phenylnaphthacene....		(76[a])
$C_{72}H_{50}$	*m*-Duodeciphenyl........		(94)
M–P. Thirteen–sixteen benzene rings:			
$C_{78}H_{54}$	*m*-Trediciphenyl.....................		(94)
$C_{84}H_{58}$	*m*-Quatuordeciphenyl		(94)
$C_{90}H_{62}$	*m*-Quindeciphenyl		(94)
$C_{96}H_{66}$	*m*-Sedeciphenyl.		(94)

[a] Visible spectrum only.
[b] Vapor-phase spectrum in medium ultraviolet (2200–4000 Å).
[c] Spectrum of solution in concentrated sulfuric acid.
[d] Spectrum of vapor in vacuum ultraviolet.
[e] Spectra of vapor, and of solution in organic solvent.
[f] Spectrum of solution at low temperature.
[g] Spectrum of solid.
[h] Spectrum of solution in concentrated sulfuric acid and in an organic solvent.
[j] Spectra of vapor, solution, and solid.
[k] Spectra of solution and solid.
All other references are to spectra of solutions in organic solvents in the medium ultraviolet.

[*] This serial number serves to characterize further the ring system by reference to *The Ring Index* of A. M. Patterson and L. T. Capell. The Reinhold Publishing Corporation, New York (1940).

[†] Several earlier measurements of the spectrum of fluorene have been omitted, as later work has shown them to be inaccurate (9), owing to the presence of unsuspected impurities, possibly acenaphthylene.

[‡] Some ambiguity concerning the numbering system of pyrene still remains. All the compounds in this table have been made to conform with the system used in this laboratory (see formula XIII), which is also that employed by Clar (47).

Attempts which have been made to establish relationships between the chemical structure of polynuclear aromatic hydrocarbons and their spectra have been successful only in certain limited cases. In a series of hydrocarbons which bear a certain structural resemblance to one another, definite and regular changes in passing from one hydrocarbon of the series to the next may sometimes be observed. Gillam and Hey (94) have examined the spectra of several p-polyphenyls (V) in which n has a value of 0, 1, 2, 3, and 4. All of these compounds possess similar spectra with a single broad maximum, the position of which is shifted to longer wave lengths as the length of the chain is increased. In the corresponding m-polyphenyl series (VI) the spectra of the members in which n has values of 1, 7, 8, 9, 10, 11, 12, 13, and 14 have been measured; here no change is observed in the position of the maximum on ascending the series, and the intensity agrees with that calculated on the assumption that each phenyl group contributes independently to the total absorption.


Va

VI
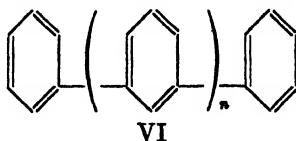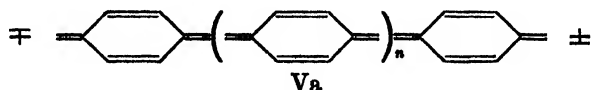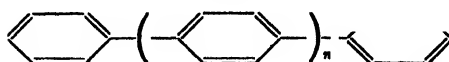
A second electronic structure (Va) may be written for the p-polyphenyls, and although this undoubtedly represents a condition of much higher energy than V, involving a separation of charge and the existence of the aromatic rings in a quinonoid form, it does permit the possibility of some resonance interaction to occur between the rings, and the p-polyphenyls can therefore be regarded as compounds of the same type as the α,ω-diphenylpolyenes (102) (VII).

VII
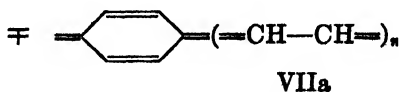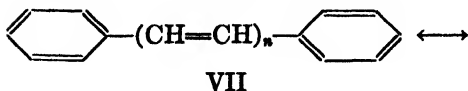
VIIa

In this latter series the quinonoid form (VIIa) differs less in energy from the benzenoid form, as only two benzenoid–quinonoid ring systems are concerned, and accordingly the α,ω-diphenylpolyenes may be considered as intermediate in character between the p-polyphenyls and the symmetrical heterocyclic carbocyanines for which two completely equivalent structures (VIII, VIIIa) can

be written (27). In the symmetrical carbocyanines the addition of an extra double bond to the chain produces an enormous bathochromic shift (1000 Å.), i.e., the position of the absorption maximum is displaced to longer wave lengths by this amount. In the α,ω-diphenylpolyenes the effect is less, and in the p-polyphenyl series it is again diminished. It therefore appears that in the two hydrocarbon series V and VII the bathochromic effect of an added group

VIIIa
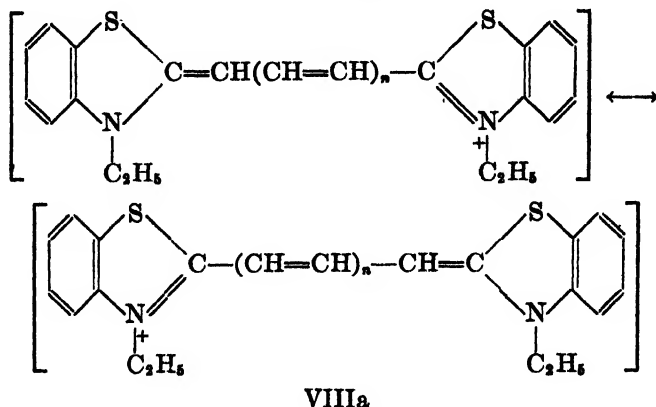
to the chain is influenced by the energy difference between the benzenoid and quinonoid structures which can be written for the molecule. In the m-polyphenyl series no bathochromic effect is observed, since meta-substitution makes a quinonoid form impossible; the linkage between the aromatic rings is completely aliphatic in character.

Some relationships between the structure and spectra can also be discerned in certain groups of hydrocarbons containing condensed aromatic ring systems. Clar (46) has examined the series benzene, naphthalene, anthracene, and naph-

| IX | X | XI | XII |
| Benzene | Naphthalene | Anthracene | Naphthacene |
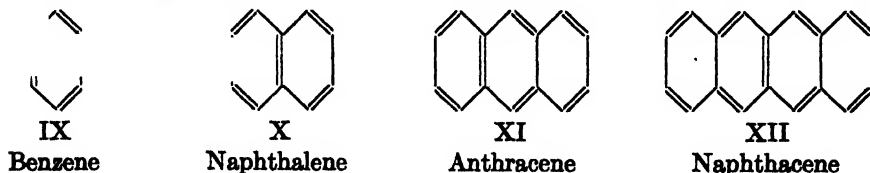
thacene (IX to XII) and has noted a progressive shift of certain regions of the spectra to longer wave lengths with the addition of each aromatic nucleus, accompanied by comparatively little change in the general appearance of the curve. The position of the absorption maximum of lowest frequency (ν_p) he finds will fit an equation of the type

where R_p is a numerical constant and n an integer. Attention is drawn to certain resemblances between this relationship and Moseley's rule for atomic

spectra. In a later series of papers (48, 49, 50) Clar extends this analysis to other types of polynuclear aromatic hydrocarbons.

The relationships between structure and spectra illustrated above apply only to carefully selected groups of compounds, and no theory of general application has yet been developed which will account for the position and intensity of the various absorption maxima in terms of the molecular or electronic structure of an aromatic hydrocarbon molecule. Förster (89), Sklar (235, 237), and Sponer and coworkers (243, 244) have attempted to calculate the position of the absorption bands of benzene by quantum-mechanical methods, but the results so far obtained do not provide a precise interpretation of the spectra. The most promising method of attack would seem to be that based on the molecular orbital concept, the general principles of which have been reviewed by Price (199). Mulliken, in a series of papers (181, 183), has discussed the application of this principle to organic compounds including benzene (182), but although these studies may lead eventually to an understanding of the fundamental mechanism of the absorption of ultraviolet radiation by the bonding electrons of the molecule, such progress as has been recorded so far is of little value to those interested primarily in the use of absorption spectra as a means of identifying molecular structures.

It should be observed that the extensive analyses of the infrared and Raman spectra of benzene and the several deuterobenzenes which have been carried out by Ingold and coworkers (6) and by Wilson (255, 256) yield information concerning the modes of vibration of the atoms in the electronic ground state of the molecule but tell nothing of the mechanism of electronic activation.

The polynuclear aromatic hydrocarbons of the type which contain condensed rings and which give rise to spectra containing much fine structure include carcinogenic substances and other compounds of biological interest. It is this type of hydrocarbon for which the spectrographic method of structure determination is most effective. The study of these compounds may be approached empirically on the assumption that each system of condensed aromatic rings gives rise to its own characteristic spectrum.[3]

In many cases where resort is made to absorption spectra as a method of structure determination, the compound of uncertain structure may be some derivative of a hydrocarbon. It is important therefore to have some knowledge of the manner and extent to which various substituents modify the spectrum of the unsubstituted hydrocarbon, for only in those cases where the introduction of a particular substituent is known not to alter the spectrum significantly can the substitution product be compared directly with alternative possible parent hydrocarbons. In this article the discussion is limited to the effect of alkyl, alicyclic, and alkene substituents on the spectra of aromatic hydrocarbons, but

[3] The differences between the spectra are in most cases sufficiently great to enable the particular ring system to be characterised directly by inspection of the absorption curve. In certain of the more complex condensed ring systems ambiguity is possible, but usually there is supporting evidence from analytical data or other sources which restrict the possible structure to one of a relatively small number of possibilities.

it is hoped that this may later be extended to include derivatives containing functional substituents, and to quinones.

As might be anticipated, more extensive investigations have been made of derivatives of benzene than of polynuclear aromatic hydrocarbons (60, 178, 180, 191, 236, 237, 251). Many substituents appear to modify the spectrum of benzene to a much greater extent than they affect those of more complex hydrocarbons; this is true particularly of their effect on the intensity of absorption. The position and intensity of the main absorption maximum of some benzene derivatives in the middle ultraviolet (180) are compared with one of the maxima

TABLE 2

Effect of substituents on the absorption spectra of benzene and 1,2-benzanthracene

SUBSTANCE	MAXIMUM		INCREASE IN INTENSITY ON SUBSTITUTION	SUBSTANCE	MAXIMUM*		INCREASE IN INTENSITY ON SUBSTITUTION
	λ	E_{molar}			λ	E_{molar}	
	$\overset{\circ}{A}.$		*per cent*		$\overset{\circ}{A}.$		*per cent*
Benzene..	2550	302		1,2-Benzanthracene.....	3410	7413	
p-Xylene........	2680	479	59	9,10-Dimethyl-1,2-benz-anthracene	3640	8710	17.5
Benzoic acid....	2670	1778	430	7-Cholanthroic acid.....	3625	7762	4.6
Phenol....	2730	1778	430	3-Hydroxy-1,2-benzan-thracene	3380	8710	17.5
Anisole..........	2720	2239	580	3-Methoxy-1,2-benzan-thracene.............	3345	7943	7.1

* Maximum H (see figure 1).

of a similar derivative of 1,2-benzanthracene (I) in table 2 (132, 133). Whereas the molecular extinction of the benzene maximum may be raised by 59 to 480 per cent by the introduction of certain substituents, the same groups raise the intensity of the 1,2-benzanthracene maximum by only 4.6 to 17.5 per cent. The benzene molecule is much more sensitive to the disturbing influence of substituents than most polynuclear aromatic hydrocarbons, probably on account of its high symmetry. In view of this, one cannot predict the effect of a substituent on the spectrum of a polynuclear aromatic hydrocarbon from analogy with the effect of the same group on the benzene spectrum.
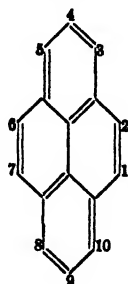
XIII

II. ALKYL DERIVATIVES

The substitution of an alkyl group for a hydrogen atom attached directly to the carbon atom of a chromophore usually produces a shift of the spectrum to longer wave lengths but does not otherwise alter the general appearance of the absorption curve. In the case of α,β-unsaturated carbonyl groups, Woodward (261) has shown that the magnitude of the bathochromic shift is independent of the position of substitution in the ethylenic double bond and is also independent of the size and nature of the alkyl group which is introduced; the shift is the same whether this be a simple methyl group or an alicyclic part of a sterol structure. In the case of the conjugated dienes both the position and the nature of the substituent modify the spectrum (26). The introduction of an alkyl substituent into a polynuclear aromatic hydrocarbon produces a bathochromic shift, but does not change the characteristic shape of the curve; the spectra of alkyl-substituted aromatic hydrocarbons may be related directly to the spectra of the corresponding unsubstituted hydrocarbon[4]. Conrad-Billroth (62) has developed a somewhat complex system of empirical rules based on a principle of vector analysis whereby the bathochromic effect produced in a given compound by certain substituents may be calculated. This was developed initially for the substitution of alkyl groups and halogens in benzene and has since been extended to naphthalene, anthracene, and pyrene derivatives (91).

Only in a few of the many series of polynuclear aromatic ring systems have a sufficient number of alkyl derivatives been examined to give some indication of the relation between the degree of bathochromic shift and the position of substitution. Askew (8) has published data on several alkylphenanthrenes, Morton and de Gouveia (176) and de Laszlo (150) on alkylnaphthalenes, Brode and Patterson (28) on alkylchrysenes, and Mayneord and Roe (169, 170) and Jones (132, 133) on alkyl-1,2-benzanthracenes.

The absorption spectrum of 1,2-benzanthracene (I), figure 1, contains twelve maxima, and the position and intensity of two of the more prominent maxima (D and H) of twenty-five alkyl and alicyclic derivatives of 1,2-benzanthracene are recorded in table 3, together with references from which fuller details of the spectra may be obtained. Inspection of table 3, supplemented by examination of the original curves, shows that in all of these derivatives the general character of the spectrum of the unsubstituted hydrocarbon is preserved. The resolution of the more prominent maxima (A B C D G H I) is not greatly influenced by the presence of the substituents, and the molar extinction coefficients of the D maximum all lie between 66,000 and 112,000, those of the H maximum between 6,000 and 10,000. The variations which are observed in the number of maxima which can be resolved are chiefly due to differences in the small bands in regions where the general slope of the absorption curve is steep (E and J), which also show greater variations in intensity than do the other maxima. Morton and de Gouveia (176) observed in the naphthalene series similar variations in maxima which occur in a general region of rapidly increasing intensity of absorption.

[4] Certain exceptions to this statement are discussed on page 32.

These variations are of a minor character and do not prejudice the value of absorption spectra as a method of characterizing ring structures, since it is the general shape of the absorption envelope rather than details of one or two particular maxima which should form a basis for the comparison of hydrocarbon

TABLE 3

Position and intensity of the D *and* H *maxima in the spectra of alkyl-1,2-benzanthracenes*
Solvent, ethanol

COMPOUND	MAXIMUM D		MAXIMUM H		NUMBER OF MAXIMA RESOLVED	REFERENCES
	λ	E_{molar}	λ	E_{molar}		
	Å.		Å.			
1,2-Benzanthracene	2870	89100	3410	7410	12	(132)
1'-Methyl-1,2-benzanthracene	2875	79400	3410	7590	11	(132)
7-Methyl-1,2-benzanthracene	2880	83200	3410	6030	13	(169)
4-Methyl-1,2-benzanthracene	2885	91200	3420	6760	11	(132)
6-Methyl-1,2-benzanthracene	2890	79400	3440	6460	11	(169)
5-Methyl-1,2-benzanthracene	2890	85100	3460	8130	12	(132)
8-Methyl-1,2-benzanthracene	2900	91200	3460	7590	12	(132)
9-Methyl-1,2-benzanthracene	2905	87100	3515	7590	9	(132)
10-Methyl-1,2-benzanthracene	2915	95500	3545	8710	12	(132)
6-Isopropyl-1,2-Benzanthracene	2895	79400	3420	6460	11	(170)
10-Isopropyl-1,2-benzanthracene	2920	112200	3530	10000	10	(169)
6,7-Dimethyl-1,2-benzanthracene	2880	93300	3430	7080	11	(169)
5,8-Dimethyl-1,2-benzanthracene	2925	85100	3520	7590	10	(132)
5,10-Dimethyl-1,2-benzanthracene	2945	85100	3580	9330	10	(132)
8,10-Dimethyl-1,2-benzanthracene	2950	91200	3560	9330	11	(132)
9,10-Dimethyl-1,2-benzanthracene	2965	79400	3640	8710	9	(132)
10-Methyl-3'-isopropyl-1,2-benzanthra-cene	2940	97700	3530	8510	10	(133)
6,7-Cyclopenteno-1,2-benzanthracene	2880	93300	3430	7080	9	(169)
5,6-Cyclopenteno-1,2-benzanthracene	2930	93300	3520	7080	10	(169)
Cholanthrene	2950	75900	3580	8910	10	(85, 170)
22-Methylcholanthrene	2960	75900	3590	7590	10	(82)
20-Methylcholanthrene	2970	89100	3590	7940	10	(169)
6-Methylcholanthrene	2975	74100	3600	9330	10	(82, 133)
6,22-Dimethylcholanthrene	2985	66100	3600	6920	10	(82, 133)
6,20-Dimethylcholanthrene	2985	95500	3600	8320	10	(82, 133)
4,10-Dimethylene-1,2-benzanthracene	2935	107000	3575	6920	12	(88)

spectra. In the naphthalene, chrysene, and phenanthrene series, the intensities of the main maxima are constant to within the same range as in the alkyl-1,2-benzanthracenes and the similarity of the shape of the absorption curve is equally well maintained.

The magnitude of the bathochromic shift produced by alkyl substitution is

influenced considerably by the position of the entering group, which usually affects all the maxima to the same relative degree. In table 3, the eight mono-methyl derivatives of 1,2-benzanthracene are arranged in order of the increasing bathochromic effect on the D maximum (figure 1); the magnitude of the effect on the H maximum is in the same order, although the shape of the absorption curve suggests that the two maxima are probably associated with different primary electronic activation processes. Substitution at the 1'-position, exerts the least effect ($\Delta_{\lambda D}$ = 5 Å.), while substitution at the meso 9- and 10-positions produces the greatest shifts ($\Delta_{\lambda D}$ = 45 Å. for 10-methyl-1,2-benzanthracene and 95 Å. for 9,10-dimethyl-1,2-benzanthracene). The spectra of the 1'-methyl derivative (XIV) and the 9,10-dimethyl derivative (XV), which represent the
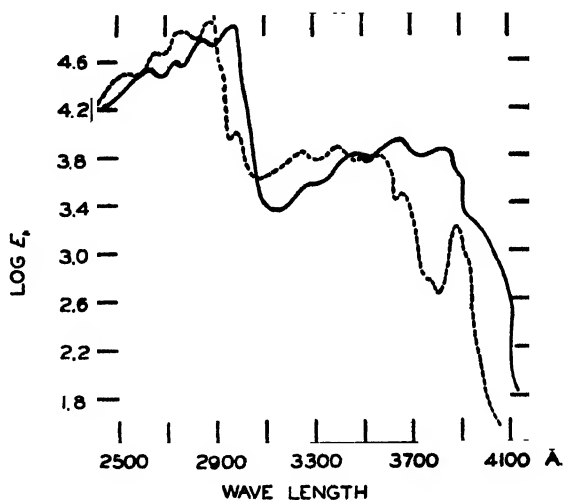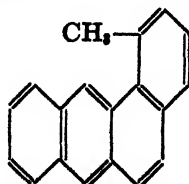

FIG. 4. Ultraviolet absorption spectra. ———, 9,10-dimethyl-1,2-benzanthracene in ethanol as solvent (132); ----, 1'-methyl-1,2-benzanthracene in ethanol as solvent (132).

methyl compounds with minimum and maximum shifts, respectively, are given in figure 4. All the other eleven monomethyl- and dimethyl-1,2-benzanthra-cenes have spectra which lie between these two curves.

XIV
1'-Methyl-1,2-benzanthracene
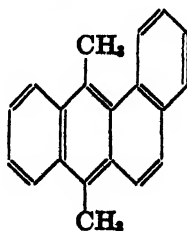
XV
9,10-Dimethyl-1,2-benzanthracene

The effect of increase in the length of the alkyl side chain has been investigated in the benzene series by Pestemer and Gübitz (189), who have recorded the spectra of all the n-alkylbenzenes up to and including the n-hexyl derivative. The fine structure of the benzene spectrum is greatly reduced in the ethyl derivative and disappears in the higher members, except for one sharp peak on the long-wave-length side of the main maximum which persists throughout the series. The increase in the bathochromic shift becomes progressively less as the side chain lengthens.

The cause of this bathochromic shift is still obscure. Mulliken, Rieke, and Brown (183), from quantum-mechanical calculations based on the concept of molecular orbitals, consider that interaction between the electrons of the ring

TABLE 4

Comparison of the position and intensity of the absorption maxima of 3-aminopyrene hydrochloride* and 3-methylpyrene†

MAXIMA	WAVE LENGTH		INTENSITY $\left(\text{Log } E_{molar}\right)$	
	—NH$_3$+	—CH$_3$	—NH$_3$+	—CH$_3$
	λ.	λ.		
A.	2330	2330	4.68	4.68
B..	2415	2415	4.92	4.94
C.	2530	2540	4.06	4.06
D...	2640	2650	4.40	4.42
E.	2745	2760	4.64	4.77
F..........	2970	2970	3.62	3.64
G	3100	3120	4.02	4.06
H......	3240	3270	4.44	4.44
I........	3400	3435	4.56	4.58
J	3530	3550	3.04	3.25
K....	3590	3620	2.86	2.90
L	3660	3680	2.56	2.64
M...	3740	3765	2.64	2.97

* Solvent 2 N hydrochloric acid in 50 per cent aqueous ethanol.
† Solvent absolute ethanol.

structure and those involved in the C—H linkages of the alkyl groups (hyperconjugation) is insufficient to account for shifts of the observed order of magnitude. Price (199) considers that the dipole effect of the alkyl group may be involved, but, if this be so, it is difficult to understand why the absorption spectra of the positive ions of aromatic amines should resemble those of the parent hydrocarbon so closely (258, 263). The polar effect of the positive charge on the nitrogen atom must produce a greater electron displacement in the —C—NH$_3$+ linkage than the relatively weak dipole displacement in the —C—CH$_3$ linkage, yet, in several cases, the —NH$_3$+ substituent has been observed to produce bathochromic shifts in aromatic hydrocarbons no larger than those produced by introduction of a methyl substituent at the same position. This is illustrated in table 4, where the wave lengths and intensities of the maxima

of 3-aminopyrene hydrochloride (XVI) and 3-methylpyrene (XVII) are compared (263).
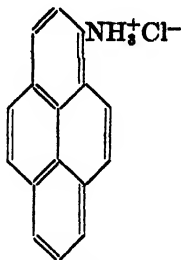
XVI
3-Aminopyrene hydrochloride
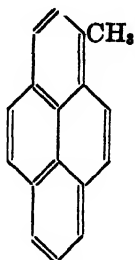
XVII
3-Methylpyrene

The positions at which the methyl group exerts its maximum bathochromic effect in the 1,2-benzanthracene series happen also to be the centers of maximum chemical reactivity in the typical aromatic substitution reactions and the positions most readily susceptible to oxidation. This suggests that the bathochromic effect of an alkyl substituent may be associated with the electron density at the point of substitution. This argument fails, however, if an attempt is made to use it to predict the effect of alkyl groups on the spectrum of chrysene.
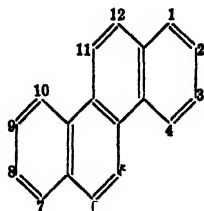
XVIII
Chrysene

Chrysene (XVIII) forms two stable quinones, 5,6- and 6,12-chrysenequinones (83). From analogy with 1,2-benzanthracene it might be predicted that the 5-methyl- and 6-methyl-chrysenes should show greater bathochromic effects than the other monomethyl derivatives. The maximum shifts are actually observed in the spectra of 4- and 5-methyl-chrysenes (28); that of 6-methyl-chrysene is considerably less. Brode and Patterson (28) suggest that the greater bathochromic shifts of the 4- and 5-methyl-chrysenes are due to steric hindrance. Considerable interference exists between the hydrogen atoms and the methyl groups at the 4- and 5-positions, which might play a part in modifying the spectra; such hindrance will be greatly increased in the case of 4,5-dimethylchrysene, where changes in the spectrum of a greater magnitude have actually been observed (134).

TABLE 5
References to the absorption spectra of alkyl derivatives of aromatic hydrocarbons

REFERENCES

A. Benzene chromophore; one benzene ring:

C_7H_8	Toluene......................	(10, 12ª, 19, 29, 61, 71, 105, 111, 112, 115, 138, 152, 160, 161, 166, 179, 180, 189, 206, 221, 249, 250, 259)
C_8H_{10}	Ethylbenzene.	(3, 10, 97, 105, 123, 160, 166, 189, 204, 205, 206, 208, 214, 215, 219, 249, 250, 258)
C_8H_{10}	o-Xylene.	(39, 61, 105, 111, 115, 138, 160, 179, 180, 204, 209, 216, 259)
C_8H_{10}	m-Xylene.	(39, 61, 105, 108, 111, 115, 138, 160, 179, 180, 221, 259)
C_8H_{10}	p-Xylene..	(29, 39, 61, 105, 109, 111, 115, 138, 160, 179, 180, 259)
C_9H_{12}	n-Propylbenzene........	(10, 71, 105, 119, 189, 197)
C_9H_{12}	1,2,3-Trimethylbenzene (hemimellitene)................	(61, 179)
C_9H_{12}	1,2,4-Trimethylbenzene (pseudocumene)...............	(10, 61, 179, 260)
C_9H_{12}	1,3,5-Trimethylbenzene (mesitylene)..	(10, 13ª, 61, 105, 198, 241, 260)
$C_{10}H_{14}$	n-Butylbenzene.....................	(10, 105, 108, 189)
$C_{10}H_{14}$	1,2,3,4-Tetramethylbenzene (prehnitene)	(61)
$C_{10}H_{14}$	1,2,3,5-Tetramethylbenzene (isodurene).......	(61, 179)
$C_{10}H_{14}$	1,2,4,5-Tetramethylbenzene (durene).	(61, 155, 179)
$C_{10}H_{14}$	1-Methyl-4-isopropylbenzene (p-cymene)	(21)
$C_{10}H_{14}$	Diethylbenzene (mixed isomers)......	(10)
$C_{11}H_{16}$	n-Amylbenzene......	(10, 105, 189)
$C_{11}H_{16}$	Pentamethylbenzene....	(61, 179)
$C_{12}H_{18}$	n-Hexylbenzene.......................	(105, 189)
$C_{12}H_{18}$	Hexamethylbenzene..................	(61, 71, 78, 106, 152, 179, 230, 231, 234)
$C_{12}H_{18}$	Triethylbenzene (mixed isomers)......	(10)
$C_{18}H_{30}$	Hexaethylbenzene............·......	(231)
$C_{24}H_{42}$	n-Octadecylbenzene..................	(108)

B. Benzene chromophore; two benzene rings:

$C_{13}H_{12}$	Diphenylmethane.....	(19, 37, 94, 106, 111, 112, 115, 152, 154, 167, 185, 197, 204, 205, 207, 215, 217, 234ᵇ, 241, 247, 249, 250)
$C_{14}H_{14}$	Dibenzyl.	(3, 7, 94, 106, 111, 153, 154, 204, 205, 212, 215, 234ᵇ, 241, 250)
$C_{16}H_{18}$	1,4-Diphenylbutane....	(204, 205, 212, 215)
$C_{16}H_{18}$	p,p'-Dimethyldibenzyl..	(213)
$C_{18}H_{22}$	1,6-Diphenylhexane....	(212, 215)
$C_{18}H_{22}$	p,p'-Diethyldibenzyl...	(213)
$C_{19}H_{24}$	Dimesitylmethane......	(241)
$C_{20}H_{26}$	1,8-Diphenyloctane.....	(215)
$C_{20}H_{26}$	sym-Dimesitylethane...	(241)
$C_{22}H_{30}$	1,4-Dimesityl-n-butane.	(241)

TABLE 5—*Continued*

COMPOUND	REFERENCES
C. Benzene chromophore; three benzene rings:	
$C_{19}H_{16}$ Triphenylmethane	(94, 112, 152, 185, 217, 234)
$C_{19}H_{16}$ Phenyl-*p*-diphenylmethane	(247, 249, 250)
D. Benzene chromophore; four benzene rings:	
$C_{25}H_{20}$ Tetraphenylmethane	(94)
E. Diphenyl chromophore:	
$C_{14}H_{14}$ 2,2'-Dimethyldiphenyl	(186)
$C_{14}H_{14}$ 3,3'-Dimethyldiphenyl	(186)
$C_{14}H_{14}$ 4,4'-Dimethyldiphenyl	(186)
$C_{16}H_{18}$ 2,2',4,4'-Tetramethyldiphenyl	(186)
$C_{18}H_{22}$ 2,2',4,4',6,6'-Hexamethyldiphenyl (dimesityl)	(186, 198)
F. Naphthalene chromophore:	
$C_{11}H_{10}$ 1-Methylnaphthalene	(104, 111, 115, 150^b, 165, 193, 248, 249)
$C_{11}H_{10}$ 2-Methylnaphthalene	(104, 111, 115, 150^b, 165)
$C_{12}H_{12}$ 1,6-Dimethylnaphthalene	(40, 150^b)
$C_{12}H_{12}$ 2,6-Dimethylnaphthalene	(40, 150^b)
$C_{12}H_{12}$ 2,7-Dimethylnaphthalene	(150^b)
$C_{13}H_{14}$ 1,3,5-Trimethylnaphthalene	(176)
$C_{13}H_{14}$ 1,3,8-Trimethylnaphthalene	(176)
$C_{13}H_{14}$ 2,3,5-Trimethylnaphthalene	(176)
$C_{13}H_{14}$ 1-Methyl-5-ethylnaphthalene	(176)
$C_{13}H_{14}$ 1-Methyl-6-ethylnaphthalene	(176)
$C_{13}H_{14}$ 1-Methyl-7-ethylnaphthalene	(176)
$C_{15}H_{18}$ 1,6-Dimethyl-4-isopropylnaphthalene (cadalene)	(176)
$C_{17}H_{14}$ 1-Benzylnaphthalene	(51, 248, 249, 250)
$C_{22}H_{18}$ *sym*-Di-1-naphthylethane	(2)
$C_{22}H_{18}$ *sym*-Di-2-Naphthylethane	(2)
G. Anthracene chromophore:	
$C_{15}H_{12}$ 2-Methylanthracene (tectonene)	(105, 202)
$C_{15}H_{12}$ 9-Methylanthracene	(253)
$C_{16}H_{14}$ 9,10-Dimethylanthracene	(253)
$C_{16}H_{14}$ 9-Ethylanthracene	(253)
$C_{17}H_{16}$ 9-Methyl-10-ethylanthracene	(253)
$C_{22}H_{26}$ 9,10-Diisobutylanthracene	(167)
H. Phenanthrene chromophore:	
$C_{15}H_{12}$ 1-Methylphenanthrene	(96)
$C_{15}H_{12}$ 9-Methylphenanthrene	(8)
$C_{16}H_{14}$ 1,2-Dimethylphenanthrene	(8)
$C_{16}H_{14}$ 1,3-Dimethylphenanthrene	(8)
$C_{16}H_{14}$ 1,7-Dimethylphenanthrene (pimanthrene)	(8)
$C_{16}H_{14}$ 1,8-Dimethylphenanthrene	(8)
$C_{16}H_{14}$ 1,9-Dimethylphenanthrene	(8, 14^a)
$C_{16}H_{14}$ 2,3-Dimethylphenanthrene	(8)
$C_{16}H_{14}$ 2,5-Dimethylphenanthrene	(8)
$C_{16}H_{14}$ 4,9-Dimethylphenanthrene	(8)
$C_{16}H_{14}$ 1-Ethylphenanthrene	(8)

TABLE 5—*Continued*

COMPOUND	REFERENCES
H. Phenanthrene chromophore:—(Continued)	
$C_{17}H_{16}$ 1,2,7-Trimethylphenanthrene..........	(8)
$C_{17}H_{16}$ 1,3,7-Trimethylphenanthrene..........	(8)
$C_{17}H_{16}$ 1,4,7-Trimethylphenanthrene..........	(8)
$C_{17}H_{16}$ 1,6,7-Trimethylphenanthrene..........	(8)
$C_{17}H_{16}$ 1,2,8-Trimethylphenanthrene (methyl-	
pimanthrene)........................	(8, 233)
$C_{17}H_{16}$ 7-Methyl-1-ethylphenanthrene (homo-	
pimanthrene)........................	(8)
$C_{18}H_{16}$ 3'-Methylcyclopentenophenanthrene....	(100, 233)
$C_{18}H_{16}$ 7-Methylcyclopentenophenanthrene....	(141)
$C_{18}H_{18}$ 1-Methyl-7-isopropylphenanthrene	
(retene).	(8)
$C_{19}H_{20}$ 1-Ethyl-7-isopropylphenanthrene	
(homoretene)........................	(8)
I. Chrysene chromophore:	
$C_{19}H_{14}$ 1-Methylchrysene.....	(28)
$C_{19}H_{14}$ 2-Methylchrysene.....	(28)
$C_{19}H_{14}$ 3-Methylchrysene.....	(28)
$C_{19}H_{14}$ 4-Methylchrysene.....	(28)
$C_{19}H_{14}$ 5-Methylchrysene.................	(28, 134)
$C_{19}H_{14}$ 6-Methylchrysene.....	(28)
$C_{20}H_{16}$ 4,5-Dimethylchrysene...........	(134)
$C_{20}H_{16}$ 5,6-Dimethylchrysene.....	(134)
J. 1,2-Benzanthracene chromophore: see table 3	
K. Pyrene chromophore:	
$C_{17}H_{12}$ 2-Methylpyrene......................	(169)
$C_{17}H_{12}$ 3-Methylpyrene	(91, 263)
$C_{17}H_{12}$ 4-Methylpyrene......	(91, 263)
L. Other chromophores:	
$C_{9}H_{10}$ o-Methylstyrene.....................	(216, 218)
$C_{10}H_{10}$ 1-Methyl-1,2-indene.................	(218)
$C_{10}H_{12}$ α-Methyl-o-methylstyrene..........	(218)
$C_{10}H_{12}$ p-Methylpropenylbenzene	(210)
$C_{11}H_{12}$ 1-Methyl-3,4-dihydronaphthalene......	(218)
$C_{14}H_{14}$ 7-Methylperinaphthene	(67, 263)
$C_{15}H_{14}$ α-Methylstilbene....................	(7, 71, 90, 152, 154, 204, 206, 214)
$C_{15}H_{14}$ p-Methylstilbene....................	(7, 152)
$C_{16}H_{16}$ α,β-Dimethylstilbene (two isomers)....	(7, 90, 146, 152, 204, 249)
$C_{20}H_{16}$ 1',10-Dimethyl-2,3-benzanthracene....	(86)
$C_{21}H_{14}$ 8(or 9?)-Methyl-3,4-benzpyrene........	(174)
$C_{21}H_{14}$ 2-Methyl-3,4-benzpyrene	(137)
$C_{22}H_{16}$ 7-Methylnaphthafluorene.............	(174)
$C_{23}H_{16}$ 2'-Methyl-1,2,5,6-dibenzanthracene....	(20)
$C_{23}H_{16}$ 3'-Methyl-1,2,5,6-dibenzanthracene....	(20)
$C_{24}H_{18}$ 7,7'-Dimethyl-2',3'-naphtho-3,4-phen-	
anthrene........................	(56)
$C_{24}H_{18}$ 9,10-Dimethyl-1,2,5,6-dibenzanthra-	
cene................................	(169)

TABLE 5—*Concluded*

COMPOUND		REFERENCES
$C_{24}H_{18}$	6,7'-Dimethyl-2',3'-naphtho-1,2-anthracene.............................	(54)
$C_{24}H_{18}$	7,7'-Dimethyl-2',3'-naphtho-1,2-anthracene	(44, 54)
$C_{25}H_{20}$	3,9,10-Trimethylpicene................	(226)
$C_{25}H_{22}$	5-Methyl-8-isopropyl-2',1'-naphtho-1,2-fluorene........................	(169) .

 ᵃ Spectrum of solution in concentrated sulfuric acid.

ᵇ Spectra of vapor and of solution in an organic solvent.

All other references are to spectra of solution in organic solvents in the medium ultraviolet.

Attempts to relate the magnitude of the bathochromic effect to steric factors in a similar manner fail completely in the 1,2-benzanthracene series. The bathochromic shift produced by a methyl substituent at the unhindered 10-position is greater than that caused by substitution at the hindered 9-position. while in 1'-methyl-1,2-benzanthracene, in which the steric relationship between the methyl group and the hydrogen at 9 is similar to that in 4-methyl- and 5-methyl-chrysenes, the observed bathochromic shift is actually *less* than for any other position which has been measured. In the spectra of 9-thiocyano- and 9-thiocyano-10-methyl-1,2-benzanthracenes the steric factors apparently do become significant, owing to the greater size of the substituent group (136). It can only be concluded that neither dipole effects, hyperconjugation, the chemical reactivity of the position of substitution, nor steric factors alone can explain adequately the relative magnitude of these bathochromic shifts.

In table 5 references to the spectra of alkyl derivatives of aromatic hydrocarbons are collected.

III. ALICYCLIC DERIVATIVES

Absorption spectra have been used extensively in the elucidation of the structure of hydrocarbons derived from natural products and in determining the positions of attack of hydrogen atoms during the partial hydrogenation of polynuclear aromatic hydrocarbons. This is illustrated in figures 5 and 6, where the absorption curves of several partial hydrogenation products of 20-methylcholanthrene and 10-methyl-1,2-benzanthracene (XIX to XXIII) are compared with the spectra of the corresponding unsubstituted aromatic parent hydrocarbons (85) (XIXa to XXIIIa). Pestemer and Manchen (193) showed that the so-called dihydropyrene and tetrahydropyrene obtained by partial hydrogenation of pyrene have spectra which are identical with those given by mixtures of 48 per cent hexahydropyrene and 52 per cent pyrene, and 75 per cent hexahydropyrene and 25 per cent pyrene, respectively, and are therefore only mixtures.
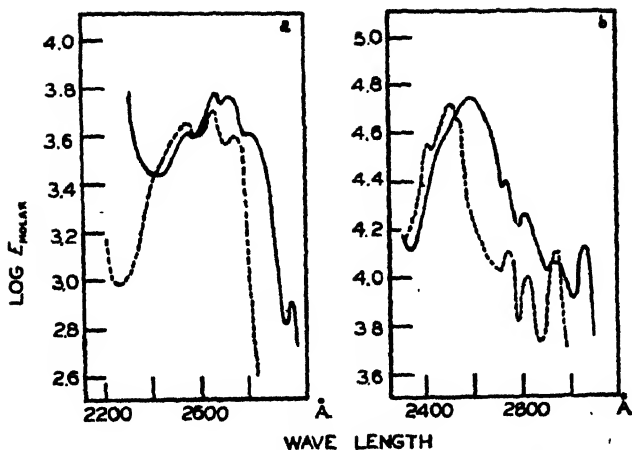
FIG. 5a. Ultraviolet absorption spectra. ——, compound XX in ethanol as solvent (85); ----, curve calculated for an equimolecular mixture of benzene and naphthalene.

FIG. 5b. Ultraviolet absorption spectra. ——, compound XXI in ethanol as solvent (85); ----, phenanthrene in ethanol as solvent (169).
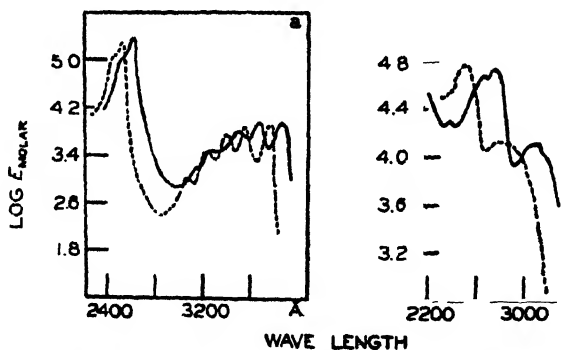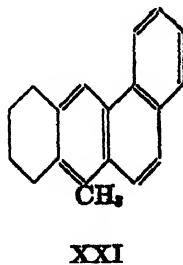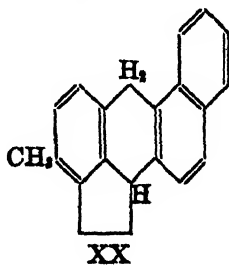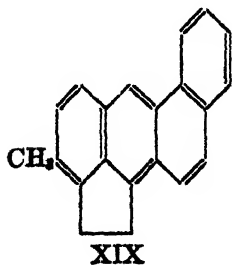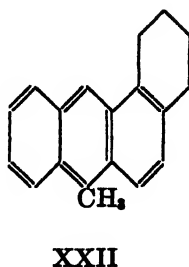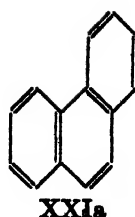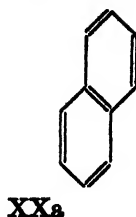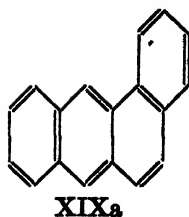

FIG. 6a. Ultraviolet absorption spectra. ——, compound XXII in ethanol as solvent (85); ----, anthracene in ethanol as solvent (169).

FIG. 6b. Ultraviolet absorption spectra. ——, compound XXIII in ethanol as solvent (85); ----, 2-phenylnaphthalene in ethanol as solvent (85).

XIX   XX   XXI

XIXa   XXa   XXIa

XXII   XXIII

XXIIa   XXIIIa
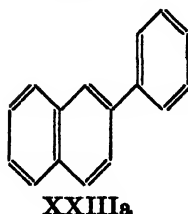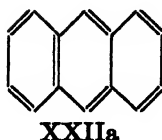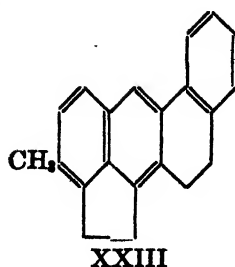
It is of considerable importance to examine the influence of alicyclic rings on the spectra of aromatic hydrocarbons, since in the use of spectra for such purposes it is assumed that the presence of alicyclic rings does not greatly alter the spectrum of the parent aromatic hydrocarbon structure.

The spectra of 5,6-cyclopenteno-1,2-benzanthracene, 6,7-cyclopenteno-1,2-benzanthracene, and of several alkyl derivatives of cholanthrene (XXIV) are included in table 3; all of these resemble the spectrum of 1,2-benzanthracene with as close a degree of similarity as is shown by the simpler alkyl derivatives, although the bathochromic shift is frequently greater than in the case of the corresponding dimethyl derivative.
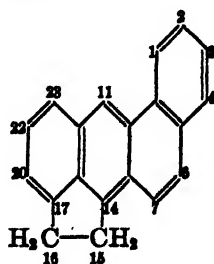
XXIV
Cholanthrene

TABLE 6

References to the absorption spectra of aromatic hydrocarbons and related compounds containing alicyclic substituents

COMPOUND		STRUCTURAL FORMULA	REFERENCES
A. Benzene chromophore:			
C_9H_{10}	Hydrindene	XXXVI	(71, 175, 204, 214, 216, 218)
$C_{10}H_{12}$	Tetralin.........................		(71, 100, 159, 176)
$C_{14}H_{12}$	9,10-Dihydroanthracene..........		(66, 155)
$C_{14}H_{18}$	1,2,3,4,5,6,7,8-Octahydro-anthracene		(33, 108, 155)
$C_{14}H_{18}$	1,2,3,4,9,10,11,12-Octahydro-phenanthrene.................		(9)
$C_{14}H_{18}$	1,2,3,4,5,6,7,8-Octahydrophen-anthrene...................		(9)
$C_{18}H_{16}$	Hexahydrochrysene (*cis* and *trans* isomers)..............	XLVII	(9)
$C_{18}H_{20}$	9,9-Diethyl-9,10-dihydroanthra-cene................		(167)
$C_{18}H_{22}$	Dodecahydrochrysene	XXV	(9)
$C_{18}H_{24}$	Dodecahydrotriphenylene........		(9, 55)
$C_{22}H_{28}$	9,9-Diisobutyl-9,10-dihydro-anthracene		(167)
$C_{22}H_{28}$	9,10-Dibutyl-9,10-dihydro-anthracene........		(167)
$C_{22}H_{28}$	9,10-Diisobutyl-9,10-dihydro-anthracene		(167)
$C_{24}H_{32}$	9,10-Diisoamyl-9,10-dihydro-anthracene		(167)
$C_{27}H_{42}$	Neoergostatriene......	XXVI	(101, 169)
$C_{30}H_{44}$	9,10-Dioctyl-9,10-dihydroanthra-cene..........................		(167)
$C_{28}H_{40}$	9,10-Di-*n*-propyl-9,10-di-*n*-butyl-9,10-dihydroanthracene........		(167)
$C_{30}H_{44}$	9,9,10,10-Tetraisobutyl-9,10-di-hydroanthracene............		(167)
$C_{34}H_{52}$	9,9,10,10-Tetraisoamyl-9,10-di-hydroanthracene..............		(167)
$C_{27}H_{40}O$	Neoergosterol....................		(69, 71, 79, 80, 127)
$C_{27}H_{40}O$	*epi*-Neoergosterol................		(71, 257)
$C_{28}H_{42}O$	*epi*-Neoergosteryl methyl ether..		(257)
$C_{18}H_{22}O_2$	$\Delta^{5,7,9}$-Estratrienol-3-one-17........		(107a)
$C_{19}H_{24}O_2$	....	XLVIII	(225)
$C_{19}H_{16}O_3$	....	XLIX	(66)
$C_{23}H_{36}O_3$	Trianhydrostrophanthidin		(79)
$C_{23}H_{28}O_3$	Trianhydroperiplogenin..........		(79)
$C_{23}H_{28}O_3$	Dihydrotrianhydrostrophan-thidin...		(79)
B. 1,2-Dihydronaphthalene chromophore:			
$C_{15}H_{18}$	1-Methyl-1,2,3,4,11,12-hexa-hydrophenanthrene		(96b)

TABLE 6—*Continued*

COMPOUND		STRUCTURAL FORMULA	REFERENCES
B. 1, 2-Dihydronaphthalene chromophore: (Cont.)			
$C_{27}H_{38}$	Neoergostapentaene	XXXa	(101, 169)
$C_{27}H_{40}$	Neoergostatetraene	XXXb	(101, 169)
$C_{18}H_{20}O$	$\Delta^{3,5,7,9}$-Estratetraeneone-17		(107a)
C. Diphenyl chromophore:			
$C_{14}H_{12}$	9,10-Dihydrophenanthrene	LIV	(9, 67, 135)
$C_{15}H_{12}$	4,5-Methylene-9,10-dihydrophenanthrene	LV	(135)
D. Naphthalene chromophore:			
$C_{12}H_{10}$	Acenaphthene		(193, 234e, 249)
$C_{13}H_{12}$	4,5-Benzhydrindene		(67, 131, 169)
$C_{14}H_{14}$	1,2,3,4-Tetrahydrophenanthrene	XXVII	(9, 98)
$C_{16}H_{16}$	Hexahydropyrene	L	(193)
$C_{17}H_{18}$	7,8-Dihydrophenalyl-7-spirocyclopentane	XXVIII	(9)
$C_{21}H_{18}$	9,10-Dihydro-22-methylcholanthrene	XX	(85e)
$C_{24}H_{20}$	9,10-Dimethyl-9,10-dihydro-1,2,5,6-dibenzanthracene		(169)
$C_{26}H_{24}$	9,9,10,10-Tetramethyl-9,10-dihydro-1,2,5,6-dibenzanthracene	XXIX	(170)
E. 1-Phenylnaphthalene chromophore: see discussion on pages 27, 34			
F. 2-Phenylnaphthalene chromophore:			
$C_{18}H_{14}$	5,6-Dihydrochrysene	XXXI	(174)
$C_{20}H_{18}$	5,8-Dimethyl-3,4-dihydro-1,2-benzanthracene	XXXII	(87)
$C_{21}H_{18}$	6,7-Dihydro-20-methylcholanthrene	XXIII	(85, 87, 131, 135)
G. Anthracene chromophore:			
$C_{19}H_{18}$	1′,2′,3′,4′-Tetrahydro-10-methyl-1,2-benzanthracene	XXII	(85)
H. Phenanthrene chromophore:			
$C_{17}H_{14}$	1,2-Cyclopentenophenanthrene		(8, 65, 100, 169)
$C_{17}H_{14}$	2,3-Cyclopentenophenanthrene		(174)
$C_{17}H_{14}$	1,10-Trimethylenephenanthrene		(51)
$C_{18}H_{16}$	2′-Methyl-1,2-cyclopentenophenanthrene		(100, 233)
$C_{19}H_{18}$	3′,7-Dimethyl-1,2-cyclopentenophenanthrene		(141)
$C_{19}H_{18}$	5,6,7,8-Tetrahydro-10-methyl-1,2-benzanthracene	XXI	(85)
$C_{16}H_{18}$	Hexahydropyrene	LI	(41)
I. 1,2-Benzanthracene chromophore:			
$C_{19}H_{12}$	1′,9-Methylene-1,2-benzanthracene	XL	(132)
$C_{20}H_{14}$	Cholanthrene	XXIV	(14d, 85, 170)
$C_{20}H_{14}$	10-Methyl-1′,9-methylene-1,2-benzanthracene		(133)

TABLE 6—*Concluded*

		STRUCTURAL FORMULA	REFERENCES

I. 1, 2-Benzanthracene chromophore: (Continued)

$C_{20}H_{14}$	4,10-Dimethylene-1,2-benzan- thracene....................	XLII	(88)
$C_{21}H_{16}$	6-Methylcholanthrene...........		(82, 133)
$C_{21}H_{16}$	20-Methylcholanthrene..........	XIX	(14[d], 169)
$C_{21}H_{16}$	22-Methylcholanthrene..........		(82)
$C_{21}H_{16}$	5,6-Cyclopenteno-1,2-benz- anthracene		(169)
$C_{21}H_{16}$	6,7-Cyclopenteno-1,2-benz- anthracene		(169)
$C_{22}H_{18}$	6,20-Dimethylcholanthrene.......		(82, 133)
$C_{22}H_{18}$	6,22-Dimethylcholanthrene.......		(82, 133)

J. Chrysene chromophore:

$C_{19}H_{12}$	4′,5-Methylenechrysene..........	XLI	(133)

K. Triphenylene chromophore:

$C_{21}H_{16}$	Cyclopentenotriphenylene........		(174)

L. 3,4-Benzpyrene chromophore:

$C_{22}H_{14}$	4,5-Dimethylene-3,4-benzpyrene.		(11)

M. Phenol chromophore:

$C_{18}H_{20}O_2$	Equilin.........................		(72, 170)
$C_{18}H_{22}O_2$	Estrone.........................		(72, 107, 170, 222, 223, 257)
$C_{18}H_{22}O_2$	Estradiol-3,17....................		(120, 128, 170)
$C_{19}H_{24}O_2$	1-Methylestradiol...............		(128)
$C_{20}H_{26}O_2$	1-Methylestradiol-17 methyl ether		(128)
$C_{20}H_{24}O_3$	Estradiol-17 acetate..............		(128)
$C_{21}H_{28}O_3$	1-Methylestradiol-17 acetate.....		(128)

N. 2-Naphthol chromophore:

$C_{27}H_{46}O$	Tetradehydroneoergosterol.......		(69, 71, 122)
$C_{18}H_{12}O_2$	Equilinin.........		(69, 72, 120)
$C_{27}H_{46}O_2$	Dihydrotetradehydroneo- ergosteryl acetate.		(257)

O. 2,3-Benzfluorenone chromophore:

$C_{20}H_{14}O$	4,4′-Trimethylene-2,3-benzfluo- renone........................		(84)

[a] The intensity of the carbonyl chromophore is too small to influence the spectrum in this compound.

[b] Spectrum covers only a restricted wave-length range.

[c] The contribution of the benzene chromophore is small.

[d] Spectrum of solution in concentrated sulfuric acid.

[e] Spectra of vapor, and of solution in an organic solvent.

The data on a large number of compounds containing alicyclic rings are summarized in table 6. The spectra of these compounds have been compared with those of the relevant parent chromophoric systems; in most cases the agreement in the appearance of the curves is sufficiently close to leave no reasonable doubt as to the nature of the chromophore present. As typical examples, the absorption curves of dodecahydrochrysene (XXV) and neoergostatriene (XXVI) are compared with that of benzene in figure 7, while those of 1,2,3,4-

tetrahydrophenanthrene (XXVII) and 7,8-dihydrophenalyl-7-spirocyclopentane (XXVIII) are compared with the naphthalene spectrum in figure 8.
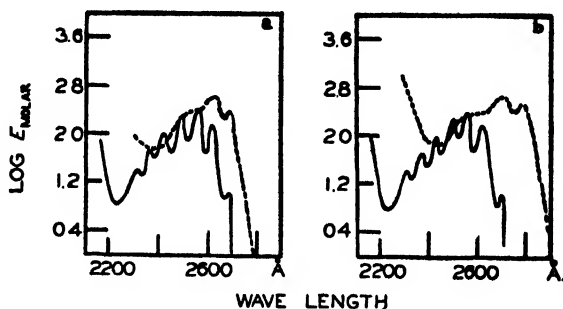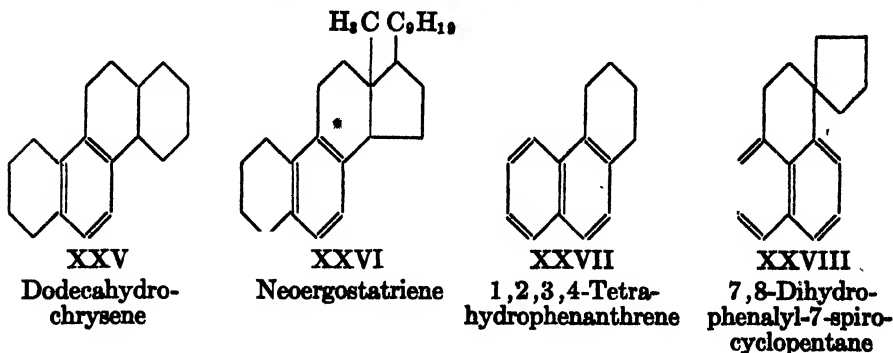
H_3C C_9H_{19}

XXV	XXVI	XXVII	XXVIII
Dodecahydro-chrysene	Neoergostatriene	1,2,3,4-Tetra-hydrophenanthrene	7,8-Dihydro-phenalyl-7-spiro-cyclopentane

FIG. 7a. Ultraviolet absorption spectra. ----, dodecahydrochrysene in ethanol as solvent (9); ——, benzene in ethanol as solvent (169).
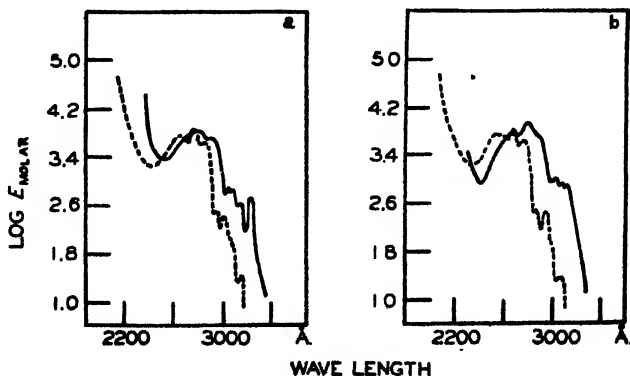
FIG. 7b. Ultraviolet absorption spectra. ----, neoergostatriene in ethanol as solvent (169); ——, benzene in ethanol as solvent (169).

FIG. 8a. Ultraviolet absorption spectra. ——, naphthalene in ethanol as solvent (9); ----, 1,2,3,4-tetrahydronaphthalene in ethanol as solvent (9).

FIG. 8b. Ultraviolet absorption spectra. ——, naphthalene in ethanol as solvent (9); ----, 7,8-dihydro-7-spirocyclopentane in ethanol as solvent (9).

The spectrographic data have been used as a criterion of structure of certain of the examples included in table 6, while in other cases the structure is known definitely from evidence not involving the spectrum. If the molecule contains two similar but separated chromophoric groups (XXIX), allowance must be made for the doubling of the absorption intensity implicit in the calculation of the molecular extinction coefficient. Certain of the chromophoric groups in-
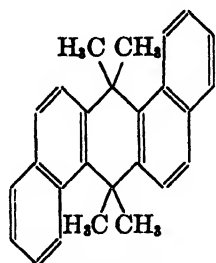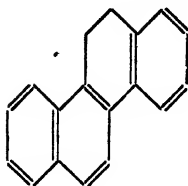

XXIX

cluded in table 6 call for further discussion. The absorption spectrum of 1,2-dihydronaphthalene (LXVII) shows a close and unexpected similarity to that of naphthalene. This chromophore occurs in neoergostatetraene (XXXa) and neoergostapentaene (XXXb) where, however, certain differences from the naphthalene spectrum are observed in the further ultraviolet. The absorption
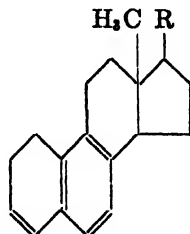
XXXa (R = C_9H_{19})
XXXb (R = C_9H_{17})

of naphthalene increases to a maximum near 2300 Å. (Log $E \approx 5$), while the spectra of XXXa and XXXb have two maxima of lower intensity in this region. Morton and de Gouveia (176) did not extend their measurements of the spectrum of 1,2-dihydronaphthalene sufficiently far into the ultraviolet to observe this region. It is evident that more data on compounds of this type are needed before it can be decided whether the differences between the naphthalene and the 1,2-dihydronaphthalene spectra are sufficient to enable a distinction between these particular unsaturated systems to be made on purely spectrographic grounds.

Certain alicyclic derivatives of 2-phenylnaphthalene (XXIII, XXXI, XXXII) have spectra which resemble that of 2-phenylnaphthalene, but the spectra of some alicyclic derivatives of 1-phenylnaphthalene (XXXIII, XXXIV) differ
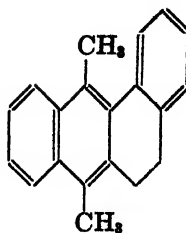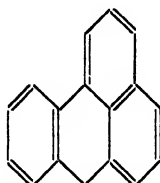
XXXI   XXXII

considerably from that of 1-phenylnaphthalene itself and thus appear to be exceptions to the rule that such substituents do not alter the spectral type. This is most probably due to the influence of steric factors, which are discussed more fully on page 32. The spectra of triphenylene (174) (XXXV) and of cyclopentenotriphenylene both resemble that of phenanthrene quite closely.
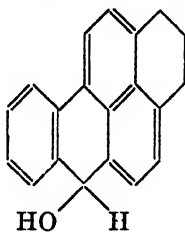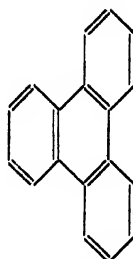
XXXIII   XXXIV   XXXV
                        HO   H   Triphenylene

In addition to the few exceptions mentioned above, minor changes in the spectra of aromatic hydrocarbons may also occur if the closure of the alicyclic ring cannot be completed without deformation of the normal bond lengths and valence angles. Presumably such deformations set up strains in the structure which may influence the spectrum by restricting the modes of vibration of the atoms and also by altering the relative energies associated with the different canonical structures contributing to the ground and excited states of the molecule. The main consequence of such strain appears to be the enhancement of the fine structure of the absorption bands, and such effects have been observed in several instances.

Ramart-Lucas and Hoch (204, 216) compared the spectra of hydrindene (XXXVI) and o-xylene (XXXVII) and observed that, although the o-xylene spectrum is devoid of fine structure, the hydrindene spectrum has two fine structure bands (figure 9). In the case of the alicyclic carbonyl compounds, both cyclobutanone and cyclopentanone exhibit fine structure in hexane solution (204, 262), while the spectra of the open-chain aliphatic ketones and the cyclic ketones with larger rings are smooth curves under the same conditions. The spectrum of 7-methylperinaphthene (263) (XXXVIII) shows structure, while that of 1-propenylnaphthalene (XXXIX) does not (figures 15 and 16).
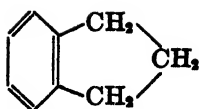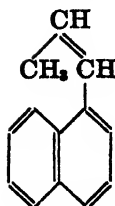
XXXVI
Hydrindene
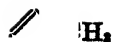
XXXVII
o-Xylene
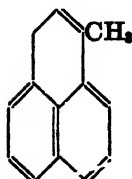
XXXVIII
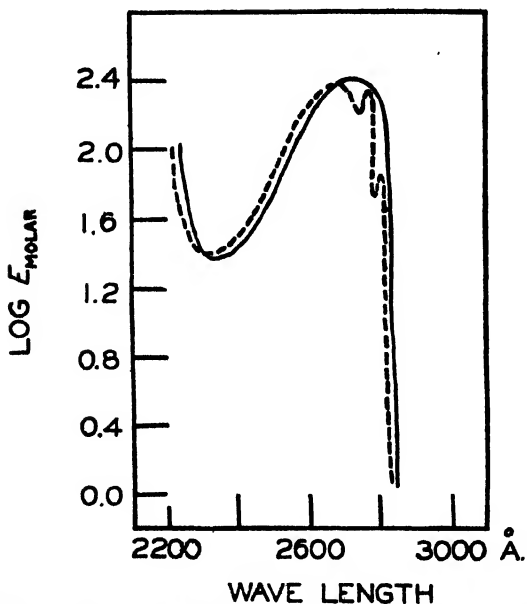7-Methylperinaphthene

XXXIX
1-Propenylnaphthalene

FIG. 9. Ultraviolet absorption spectra. ——, o-xylene in hexane as solvent (216); ----, hydrindene in hexane as solvent (216).

Striking examples of this effect are provided by 1′,9-methylene-1,2-benzanthracene (XL) and 4,5-methylenechrysene (XLI), both of which exhibit very highly developed fine structure. In XL there is also a change in the character of the absorption in the region between 2800 and 3000 Å., where the D maximum of 1,2-benzanthracene (figure 1) is replaced by a system of two maxima of lower intensity (figure 10a). The introduction of the bridge methylene group involves a deformation of the bond angles by about 12° to close the five-membered ring,
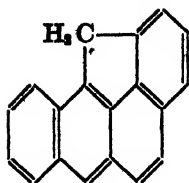
XL

1',9-Methylene-1,2-benzanthracene
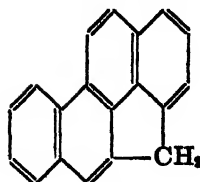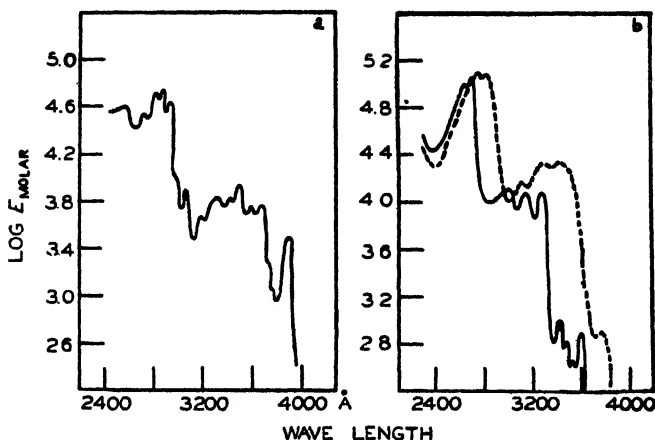
XLI

4,5-Methylenechrysene

FIG. 10a. Ultraviolet absorption spectrum of 1',9-methylene-1,2-benzanthracene in ethanol as solvent (132).

FIG. 10b. Ultraviolet absorption spectra. ——, 4,5-methylenechrysene in ethanol as solvent (134); ----, 4,5-dimethylchrysene in ethanol as solvent (134).

assuming a planar structure for the molecule. In fluorene (124, 125) there is evidence from dipole-moment measurements that, in solution, this strain is distributed among the aromatic as well as the aliphatic bonds, but no information is available concerning the molecular geometry of XL and XLI. Although the dimethylene bridge of 20-methylcholanthrene and of cholanthrene does not produce this effect, it has recently been observed that in 4,10-dimethylene-1,2-benzanthracene (XLII) (72) there is more structure present in the 3000–4000 Å. region than in the parent hydrocarbon.
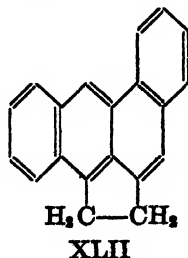
XLII

4,10-Dimethylene-1,2-benzanthracene

The alicyclic derivatives XL and XLI may be regarded as derivatives of fluorene. The spectra of several other hydrocarbons related to fluorene have been regarded as of a distinct chromophoric type and are included in table 1; among these are 1,2-benzfluorene (XLIII), 3,4-benzfluorene (XLIV), 1,2,5,6-dibenzfluorene (XLV), and 1′,2′-naphtho-2,3-fluorene (XLVI), which may be considered as methylene derivatives of 2-phenylnaphthalene, 1-phenylnaphthalene, 1,2′-dinaphthyl, and 2-phenylphenanthrene, respectively. The spectra
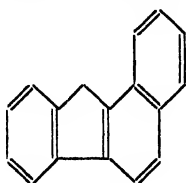
XLIII
1,2-Benzfluorene
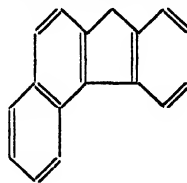
XLIV
3,4-Benzfluorene
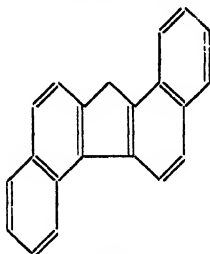
XLV
1,2,5,6-Dibenzfluorene
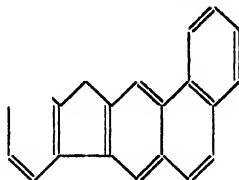
XLVI
1′,2′-Naphtho-2,3-fluorene

of XLIII and XLIV differ markedly from the spectra of the respective parent aromatic hydrocarbons; the spectra of the parent hydrocarbons corresponding to XLV and XLVI have not been measured. In all of these substances, the methylene linkage holds together two parts of the molecule which would otherwise be joined only by a single carbon-to-carbon bond; consequently, the addition of the methylene group must greatly modify the rigidity of the molecule. In 4,5-methylenechrysene and 1′,9-methylene-1,2-benzanthracene the methylene linkage is attached to a system of condensed aromatic rings in which there is already very great steric restriction, and accordingly it is not surprising that the introduction of the methylene bridge causes much greater changes in the spectra of structures such as XLIII to XLVI than in XL and XLI.

XLVII

XLVIII

XLIX

LI

WAVE LENGTH
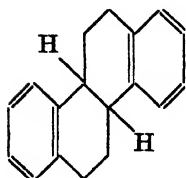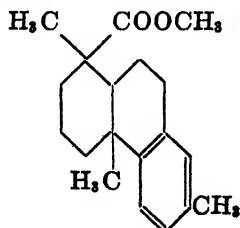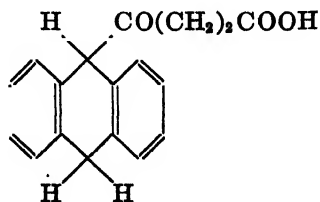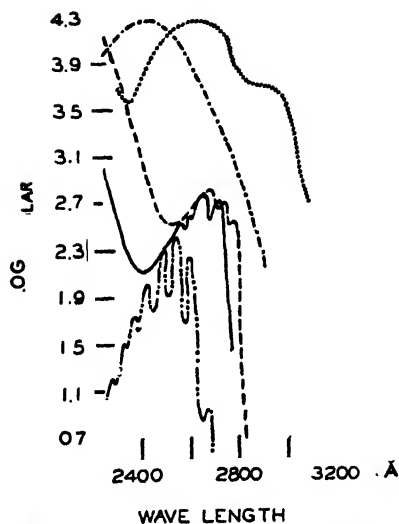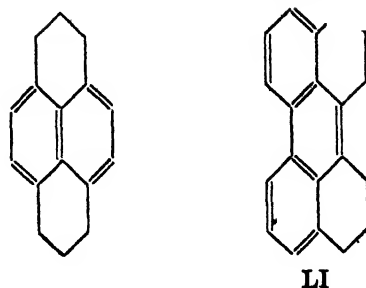
FIG. 11. Ultraviolet absorption spectra. ———, 2 moles of mesitylene in ethanol as solvent; ----, dimesityl in ethanol as solvent (198); —·—·, diphenyl in methanol as solvent (154); ····, 9,10-dihydrophenanthrene in ethanol as solvent (135); —··—··, benzene in ethanol as solvent (169).

IV. ARYL DERIVATIVES

Several of the polynuclear aromatic hydrocarbons listed in table 1 may be regarded as aromatic hydrocarbons containing aryl substituents. The simplest of these is diphenyl.

A comparison of the spectra of diphenyl and benzene shows that they differ greatly from one another (figure 11), and considerable interaction must take place between the electronic systems of the two aromatic rings across the coannular bond, which cannot have the purely aliphatic character suggested by the conventional formula (LIIa). Evidence of this is provided also by x-ray diffraction measurements (70), which show that the length of the coannular bond is 1.48 Å. in comparison with 1.54 Å. for the aliphatic carbon–carbon link and 1.39 Å. for

a purely aromatic bond (22). It has been inferred that the coannular linkage in diphenyl has considerable double-bond character and that structures of the type LIIb and LIIc are contributing significantly to the ground state of the molecule (32).

LIIa   LIIb   LIIc
Diphenyl
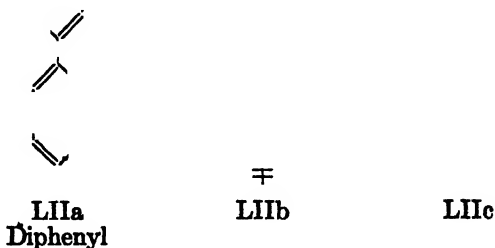
Studies of the spectra of alkyl derivatives of diphenyl (186, 198) have shown that such groups may be introduced at the meta and para positions without changing the spectrum, apart from producing the normal bathochromic shift and minor changes in intensity. Substitution of methyl groups at the ortho positions, on the other hand, causes a profound change in the spectrum; thus the spectrum of dimesityl (LIII) resembles that of mesitylene rather than that

LIII
Dimesityl
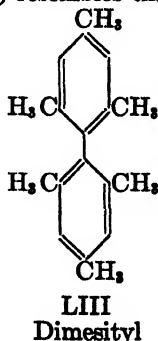
of diphenyl (figure 11). Structures such as LIIb and LIIc must be planar, and if, owing to steric interference, the two benzene rings are prevented from taking up a coplanar configuration, the contributions of these resonance forms to the molecular structure will be greatly reduced, and substances that contain ortho substituents behave as though the coannular bond were very largely aliphatic in character. This explanation of the anomalous effect of methyl substituents at the ortho positions is supported by the fact that the spectra of 9,10-dihydrophenanthrene (LIV) and 4,5-methylene-9,10-dihydrophenanthrene (LV) (135), in which the ortho-substituted methylene and dimethylene bridges hold the two aromatic rings in or near a coplanar configuration, possess the diphenyl type of spectra.

LIV
9,10-Dihydrophenanthrene

LV
4,5-Methylene-
9,10-dihydrophenanthrene
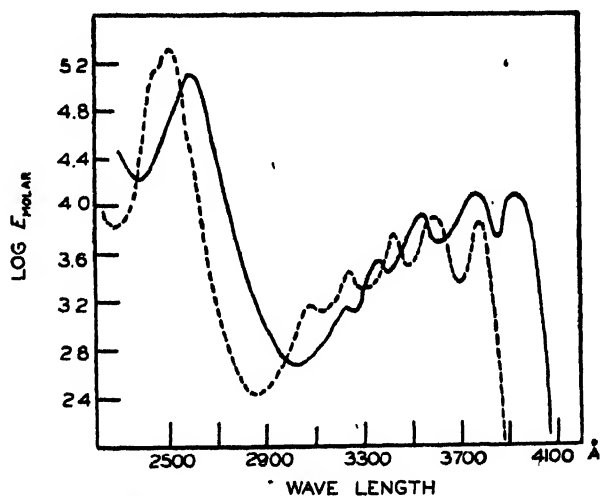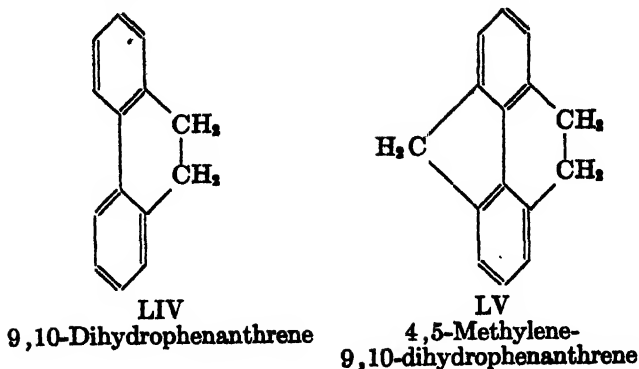
FIG. 12. Ultraviolet absorption spectra. ——, 9,10-diphenylanthracene in ethanol as solvent (202); ----, anthracene in ethanol as solvent (169).

The spectra of several aryl-substituted polynuclear aromatic hydrocarbons exhibit effects which can be attributed to steric factors that act to prevent the aryl substituents from taking up a configuration coplanar with the rest of the conjugated system. The spectra of 9-phenylanthracene (LVI), 9,10-diphenylanthracene (LVII) (figure 12), a.id 9,10-di(1-naphthyl)anthracene (LVIII) are all very similar to that of unsubstituted anthracene (135), in spite of the very considerable change in the nature of the unsaturated system. Steric interference may occur in these compounds between the hydrogen atoms of the ortho positions of the meso-aryl substituents and the hydrogen atoms at the 1- and 8-positions of the anthracene ring system. Theoretically such compounds might be expected to possess spectra equivalent to the summation of the spectra of the meso-aryl substituents and anthracene. In the case of the phenyl derivatives the intensity of the benzene contribution is negligible. The di(1-naphthyl)
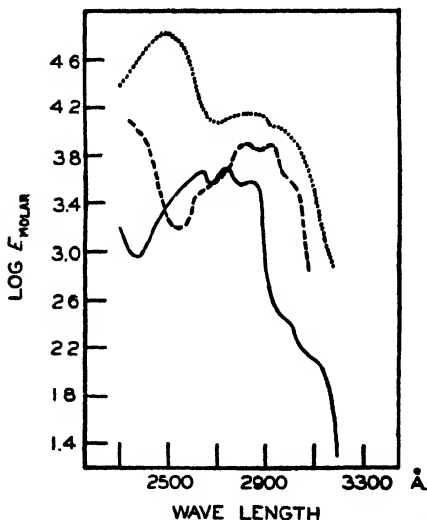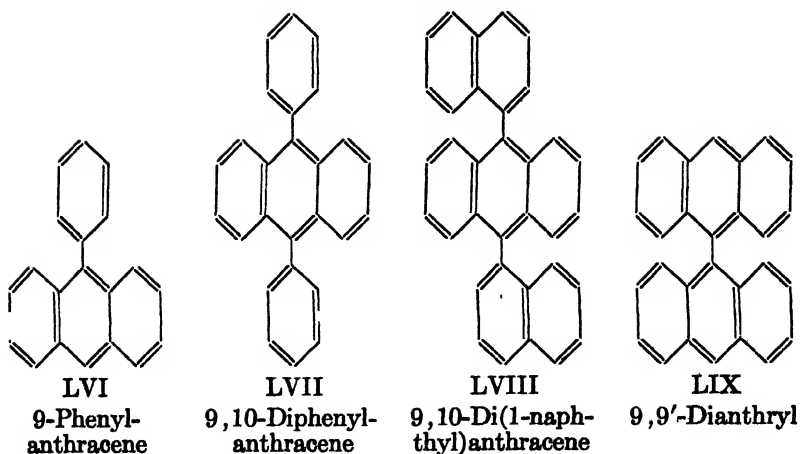
FIG. 13. Ultraviolet absorption spectra. ——, curve calculated for 1 mole of naphthalene and 1 mole of benzene; ----, 1-phenylnaphthalene in ethanol as solvent (131); ····, 2-phenylnaphthalene in ethanol as solvent (135).

derivative does show some structure which has been attributed to the naphthalene component (135), while the intensity of the absorption of 9,9'-dianthryl (LIX) is very close to twice that of anthracene.

Further examples of this effect are provided by the similarity between the spectra of phenanthrene and 9,9'-diphenanthryl (LX) (116) and between those of 1-phenylnaphthalene and an equimolecular mixture of naphthalene and benzene (figure 13). In the case of 2-phenylnaphthalene (XXIIIa), where there is no steric restriction, the spectrum differs greatly from that calculated on the assumption that the benzene and naphthalene chromophores behave inde-

pendently. The similarity between the spectra of 2-phenylnaphthalene and 6,7-dihydromethylcholanthrene (XXIII) (85, 135) may be cited as evidence in support of an approximately planar structure for 2-phenylnaphthalene (figures 6b and 13), because in 6,7-dihydromethylcholanthrene the phenyl group is held in or near the plane of the naphthalene ring by a dimethylene bridge.
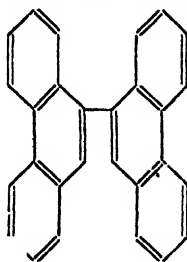
LX
9,9′-Diphenanthryl

V. ALKENE, CYCLOALKENE, AND ALKYNE DERIVATIVES

Very little information is available concerning the effect of alkene side chains on the spectra of aromatic hydrocarbons, and that is restricted almost entirely to the benzene and the naphthalene series. Ramart-Lucas (204) compared the spectra of LXI, LXII, LXIII, and LXIV, and observed that the spectrum only differs appreciably from that of ethylbenzene in the case of LXI, where the ethylenic link is conjugated with the aromatic system. In the case of LXI, however, the change is considerable, the intensity increases more than tenfold

LXI
Vinylbenzene

LXII
Allylbenzene

LXIII

LXIV
Ethylbenzene

LXV
1-Propenylbenzene
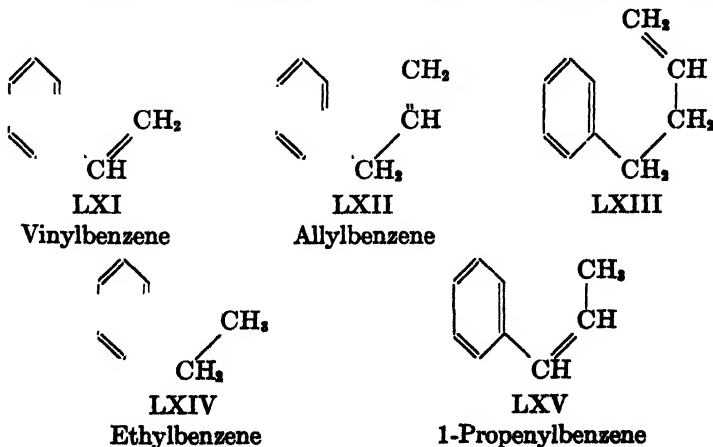
in the region near the maximum (figure 14). Similar observations have been recorded by Hillmer and Schorning (119), who compared the spectra of allylbenzene (LXII) and 1-propenylbenzene (LXV). The spectrum of 1,4-dihydronaphthalene (LXVI) is benzenoid, while that of 1,2-dihydronaphthalene (LXVII) is not (176).

LXVI   LXVII

1,4-Dihydronaphthalene   1,2-Dihydronaphthalene

In view of the fact that substituents usually modify the spectrum of benzene to a greater extent than they influence those of polynuclear aromatic hydro-
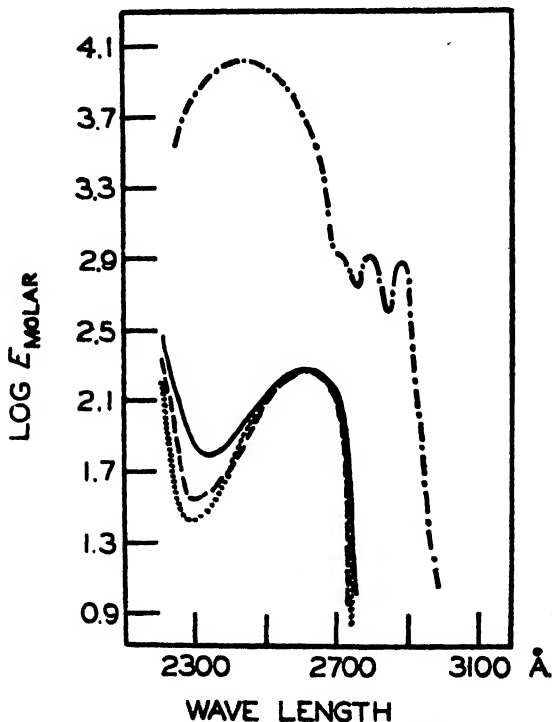
FIG. 14. Ultraviolet absorption spectra. ——, allylbenzene in ethanol as solvent (204); ----, 4-phenyl-1-butene in ethanol as solvent (204); ····, ethylbenzene in ethanol as solvent (204); —·—·, styrene in ethanol as solvent (204).

carbons, it may be anticipated that the introduction of conjugated alkene substituents into polynuclear hydrocarbons may produce less pronounced effects. The spectra of 1-allylnaphthalene (LXVIII), 1-methylnaphthalene, and 1-propenylnaphthalene (LXIX) are compared in figure 15 (193). The effect of conjugation of the side-chain double bond with the naphthalene ring is less marked than its influence on the benzene chromophore; it may be noted that the conjugated compound shows no fine structure. Closure of the side chain to form a ring, as in 7-methylperinaphthene (67, 236) (XXXVIII), leads to a

considerable bathochromic shift and the appearance of fine structure. In acenaphthylene (LXX), in which the alkene substituent is conjugated with the

LXVIII
1-Allylnaphthalene

LXIX
1-Propenylnaphthalene

LXX
Acenaphthylene
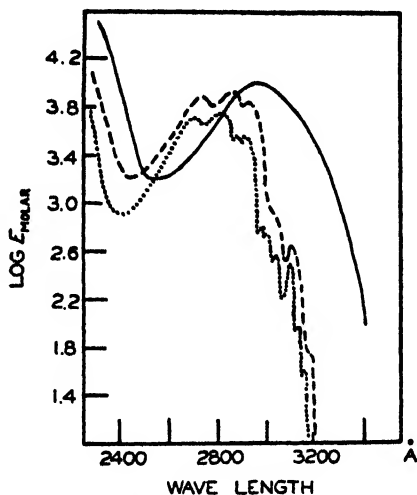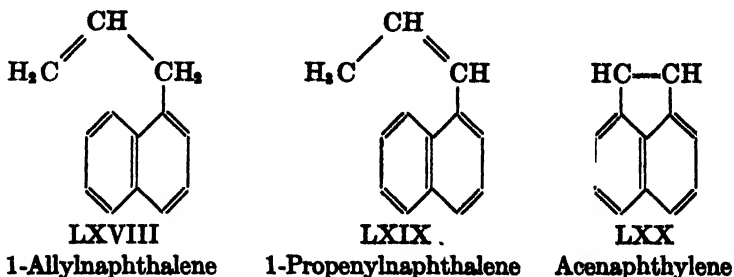
FIG. 15. Ultraviolet absorption spectra. ——, 1-propenylnaphthalene in ethanol as solvent (197); ----, 1-allylnaphthalene in ethanol as solvent (193); ·····, 1-methylnaphthalene in ethanol as solvent (193).

naphthalene system at two points, the spectrum differs considerably, particularly at wave lengths below 2800 Å. (figure 16). The variations among these alkene naphthalene derivatives are of interest, but as yet there are insufficient data for any general conclusions to be drawn from them which might be of value in the elucidation of the structure of unknown compounds which may belong to one of these types.

The spectra of two interesting substances containing cycloalkene substituents, 9-cyclohexenylphenanthrene (LXXI) and 9-cyclopentenylphenanthrene (LXXII), have been reported by Henri and Bergmann (116), who observe that LXXII has a spectrum which differs considerably from that of phenanthrene, as would be anticipated in view of the altered conjugated system. The cyclohexenyl derivative (LXXI) has a spectrum which is very similar to that
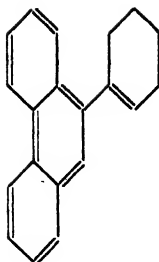
LXXI   LXXII
9-Cyclohexenylphenanthrene   9-Cyclopentenylphenanthrene
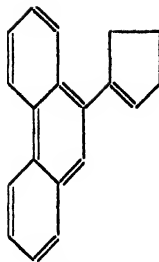
of phenanthrene.   Calvin (32) considers that steric factors of the type discussed on page 32 may account for this difference; it may be possible, however, that the double bond in LXXI has moved out of conjugation with the aromatic
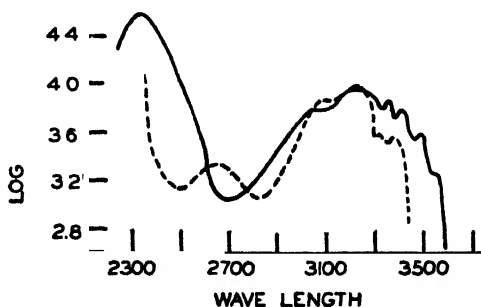
Fig. 16. Ultraviolet absorption spectra. ——, 7-methylperinaphthene in ethanol as solvent (263); ----, acenaphthene in ethanol as solvent (67).

ring during the synthesis.   Bergmann and Bergmann (16) cite evidence against this hypothesis which does not definitely exclude it.

In compounds such as LXII and LXVIII, where the side-chain double bond is "insulated" from the aromatic system by one or more methylene groups, there can be no doubt that it makes an additive contribution to the total absorption of the molecule; this, however, will occur in the vacuum ultraviolet region.   If the side chain should contain a conjugated diene separated from the aromatic system, its additive contribution should be considerable; an example of this is provided by 1,4-dibenzylbutadiene (71, 238) (LXXIII).   Where the
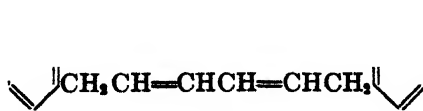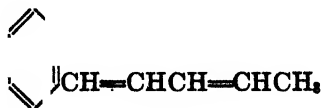
LXXIII   LXXIV
1,4-Dibenzylbutadiene   1-Phenyl-1,3-pentadiene

TABLE 7

References to the absorption spectra of aromatic hydrocarbons containing alkene and cycloalkene substituents

COMPOUND		REFERENCES
A. Benzene derivatives:		
C_8H_8	Styrene	(3, 7, 13[a], 71, 95, 97, 123, 143, 153, 191, 197, 204, 205, 206, 208, 211, 238)
C_9H_8	Indene	(71, 175, 207, 216, 218, 245)
C_9H_{10}	Allylbenzene	(3, 71, 119, 197, 204, 205, 207, 210, 211)
C_9H_{10}	Propenylbenzene	(71, 119, 197, 206, 207, 210)
C_9H_{10}	o-Methylstyrene	(216, 218)
C_9H_{10}	2-Phenyl-1-propene	(211)
$C_{10}H_{10}$	1,2-Dihydronaphthalene	(176, 218)
$C_{10}H_{10}$	1,4-Dihydronaphthalene	(176)
$C_{10}H_{10}$	1-Methyl-1,2-indene	(218)
$C_{10}H_{10}$	1-Phenyl-1,3-butadiene	(238)
$C_{10}H_{12}$	α-Methyl-o-methylstyrene	(218)
$C_{10}H_{12}$	4-Phenyl-1-butene	(3, 204, 205, 211)
$C_{10}H_{12}$	4-Methylpropenylbenzene	(210)
$C_{11}H_{12}$	1-Methyl-3,4-dihydronaphthalene	(218)
$C_{11}H_{12}$	1-Phenyl-1,3-pentadiene	(197)
$C_{11}H_{14}$	5-Phenyl-1-pentene	(211)
$C_{12}H_{14}$	2,3,4,5-Tetrahydrodiphenyl	(197)
$C_{12}H_{14}$	6-Phenyl-1-hexene	(211)
$C_{13}H_{16}$	1-Ethylidene-2,2-dimethylhydrindene	(218)
$C_{13}H_{18}$	7-Phenyl-1-heptene	(211)
$C_{14}H_{12}$	cis-Stilbene	(7, 90, 151, 154, 239)
$C_{14}H_{12}$	trans-Stilbene	(7, 37, 71, 90, 94, 106, 111, 118, 151, 152, 153, 154, 206, 210, 214, 238, 239, 249)
$C_{14}H_{12}$	asym-Diphenylethylene	(31, 111, 156, 210, 232)
$C_{14}H_{18}$	1-Ethylidene-2,2-dimethyltetralin	(218)
$C_{15}H_{12}$	9-Ethylidenefluorene	(217)
$C_{15}H_{14}$	α-Methylstilbene	(7, 71, 90, 152, 154, 204, 206, 214)
$C_{15}H_{14}$	p-Methylstilbene	(7, 152)
$C_{15}H_{14}$	1-Phenyl-1-(p-tolyl)ethylene	(204, 210)
$C_{15}H_{14}$	1-Phenyl-2-(p-tolyl)ethylene	(210)
$C_{15}H_{14}$	1,1-Diphenyl-1-propene	(210)
$C_{15}H_{14}$	1,2-Diphenyl-1-propene	(210)
$C_{16}H_{12}$	Benzylideneindene	(175)
$C_{16}H_{14}$	1,4-Diphenyl-1,3-butadiene	(37, 71, 92, 102, 105, 106, 111, 118, 201, 238)
$C_{16}H_{16}$	α,β-Dimethylstilbene (two isomers)	(7, 90, 146, 152, 204, 249)
$C_{16}H_{16}$	sym-Dibenzylethylene	(71, 154, 238)
$C_{16}H_{16}$	Distyrene	(97)
$C_{16}H_{16}$	2,3-Diphenyl-2-butene (two isomers)	(220)
$C_{16}H_{24}$	n-Octylstyrene	(211)
$C_{18}H_{14}$	3,3'-Diindenyl	(245)
$C_{18}H_{14}$	Cinnamylideneindene	(175)
$C_{18}H_{16}$	1,6-Diphenyl-1,3,5-hexatriene	(71, 102, 105, 201, 238)

TABLE 7—*Concluded*

REFERENCES

$C_{18}H_{18}$	1,4-Dibenzyl-1,3-butadiene.................	(71, 238)
$C_{20}H_{18}$	1-Styrylacenaphthalene......................	(263)
$C_{20}H_{16}$	Triphenylethylene..........................	(7, 19, 206)
$C_{20}H_{18}$	1,8-Diphenyl-1,3,5,7-octatetraene..........	(71, 102, 105, 201, 238)
$C_{20}H_{20}$	1,6-Dibenzyl-1,3,5-hexatriene...............	(71, 238)
$C_{22}H_{20}$	1,10-Diphenyl-1,3,5,7,9-dodecapentaene.....	(71, 102, 238)
$C_{24}H_{22}$	1,12-Diphenyl-1,3,5,7,9,11-dodecahexaene...	(71, 102, 105, 201, 238)
$C_{26}H_{16}$	Dibiphenyleneëthylene..................:..	(33, 245)
$C_{26}H_{20}$	Tetraphenylethylene........................	(7, 102, 154, 249)
$C_{26}H_{24}$	1,14-Diphenyl-1,3,5,7,9,11,13-tetradecaheptaene.....................................	(71, 102, 238)
$C_{28}H_{20}$	1-Phenyl-3-diphenylmethyleneindene........	(23)
$C_{30}H_{22}$	2,8-Diphenyl-6b,12b-dihydrochrysene.......	(168)
$C_{30}H_{24}$	3-Diphenylmethylene-1,5-diphenyl-1,4-pentadiene.....................................	(156)
$C_{34}H_{28}$	3-Diphenylmethylene-1,5-distyryl-1,4-pentadiene.....	(156)
$C_{35}H_{25}$	Pentaphenylcyclopentadienal.................	(262)
$C_{34}H_{26}$	1,12-Diphenyl-4,6,7,9-diphenylene-1,3,5,7,9,11-dodecahexaene................	(245)

B. Naphthalene derivatives:

$C_{12}H_{8}$	Acenaphthylene............................	(67)
$C_{13}H_{12}$	1-Allylnaphthalene	(193)
$C_{13}H_{12}$	1-Propenylnaphthalene.....................	(193)
$C_{14}H_{14}$	7-Methylperinaphthene......................	(67, 263)
$C_{20}H_{16}$	1-Phenyl-4-(1)-naphthyl-1,3-butadiene.......	(92)

C. Derivatives of other aromatic hydrocarbons:

$C_{19}H_{16}$	9-Cyclopentenylphenanthrene...............	(32, 116)
$C_{20}H_{18}$	9-Cyclohexenylphenanthrene...............	(32, 116)
$C_{36}H_{24}$	3,9-Diphenyldivinylperylene................	(195)

D. Cumulene derivatives:

$C_{28}H_{20}$	Tetraphenyl-1,2,3-butatriene...............	(23, 145)
$C_{30}H_{18}$	Tetraphenyl-1,2,3,4,5-hexapentaene........	(145)
$C_{30}H_{20}$	Dibiphenylene-1,2,3,4,5-hexapentaene......	(145)

* Spectrum of solution in concentrated sulfuric acid.

TABLE 8

References to the absorption spectra of aromatic hydrocarbons containing alkyne substituents

REFERENCES

$C_{8}H_{8}$	Phenylacetylene.....................................	(123, 177)
$C_{14}H_{10}$	Diphenylacetylene (tolane).........................	(58, 102)
$C_{16}H_{10}$	Diphenyldiacetylene...............................	(102)
$C_{16}H_{14}$	4,4′-Dimethyltolane...............................	(58)
$C_{18}H_{18}$	4,4′-Diethyltolane................................	(58)
$C_{18}H_{18}$	3,3′,4,4′-Tetramethyltolane........................	(58)
$C_{20}H_{22}$	4,4′-Di-*n*-propyltolane.............................	(58)
$C_{22}H_{26}$	4,4′-Di-*n*-butyltolane..............................	(58)

diene side chain is conjugated with the aromatic system it produces profound changes in the chromophore, e.g., 1-phenyl-1,3-pentadiene (LXXIV) (197). In the α,ω-diphenylpolyenes (VII), which have been investigated intensively by Hausser, Kuhn, and Seitz (102) and by Rădulescu and Bărbulescu (201), the long polyene chain appears to be the major factor in the light absorption process, since the spectra differ little in type from those of the carotenoid pigments in which the phenyl groups are replaced by aliphatic end groups.

Aromatic hydrocarbons containing alkene chains provide possibilities of *cis-trans* isomerism. The spectra of *cis-* and *trans*-stilbenes have been investigated by Arends (7), by Smakula and Wassermann (239), and, most recently, by Lewis, Magel, and Lipkin (151). Considerable differences are observed between the spectra of the two isomers. Lewis and coworkers have discussed these differences and their bearing on the photoconversion of one isomer into the other (151). Ramart-Lucas (204) examined the spectra of several pair of *cis-trans* isomers outside the hydrocarbon field and concluded that, although the spectra of such isomers frequently exhibit differences, it seems unlikely that the absolute configurations of the two isomers can be deduced from their ultraviolet absorption spectra alone.

References to the spectra of alkene, cycloalkene, and alkyne derivatives of aromatic hydrocarbons are summarized in tables 7 and 8; so few alkyne-substituted aromatic hydrocarbons have been examined that it is not possible to draw any general conclusions concerning the effect of such groups on the spectra.

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(263) Unpublished observation from this laboratory.

CHEMISTRY OF THE BIOLOGICALLY IMPORTANT IMIDAZOLES[1]

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CONTENTS

I. INTRODUCTION

The imidazoles include many substances of both biological and chemical interest. Of special significance are the purines, proteins, and other imidazoles discussed in this review. Inasmuch as the imidazole moiety is part of a fused-ring system in the purines, these compounds have been excluded from consideration here. The imidazole content of protein is due chiefly to histidine, which is separately discussed. The isolation, structure determination, and synthesis of biological imidazoles are reviewed in the following sections. Only occasional references to important physiological, biochemical, and pharmacological attributes are made, since these latter are thoroughly treated in Guggenheim's *Die biogenen Amine* (45a).

Speculation on the biogenesis of the imidazoles would lead one to believe that the simpler metabolic intermediates arise from natural sugars and ammonia. This type of synthesis has its laboratory counterpart (29, 80, 103, 108), and is a kind of process for which the intermediates should be readily available phytochemically. For instance, known sugar metabolites might react as follows:

$$\text{Carbohydrate} \longrightarrow \text{RCOCHO} \xrightarrow[\text{HCHO}]{\text{NH}_3}
\begin{array}{c}
\text{RC—NH} \\
\parallel \qquad \diagdown \\
\qquad \qquad \text{CH} \\
\mid \qquad \diagup\!\!\diagup \\
\text{HC—N}
\end{array}$$
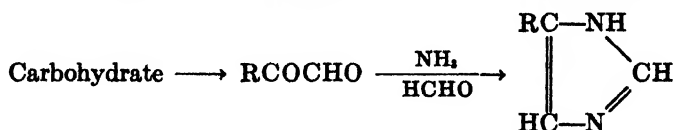
After conversion to histidine, the imidazole is incorporated into protein. Alkaloids containing the imidazole nucleus may also arise as conversion products of histidine, as well as of other amino acids, such as arginine (compare page 57). The structure of the purines is sufficiently complex to suggest that they result from elaboration of the imidazole molecule from ingested histidine.

The prototype of the group, imidazole, was first observed by Debus (29) in reacting ammonia and glyoxal. This reaction was responsible for the alternative name for imidazole, i.e., glyoxaline. Hantzsch (49) later suggested the use of the name imidazole. Both names are very common in the literature, but imidazole has been given official recognition (81).

The numbering of the imidazole ring begins with the nitrogen atom bearing a hydrogen atom.

$$\begin{array}{c}
\text{H} \\
\text{C} \\
\diagup\!\!\diagup\,^2\diagdown \\
\text{N}^3 \qquad {}^1\text{NH} \\
\mid \qquad \quad \mid \\
\text{HC}=\!=\!=\text{CH}
\end{array}$$
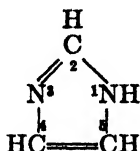
In the case of some imidazoles monosubstituted on either the 4- or the 5-carbon atom, the designation 4 (or 5) is employed, since decision as to where the group is attached has not been made. A mathematical treatment of the corresponding resonance forms of histidine has been published (58).

II. BETTER-KNOWN NATURALLY OCCURRING IMIDAZOLES

A. Anserine

In 1929 Ackermann and coworkers (6) announced the discovery of a new, nitrogenous component of goose muscle. This compound proved to be basic, possessed the empirical formula $C_{10}H_{16}N_4O_3$, and was given the name anserine. Its aqueous solution was alkaline; anserine could be precipitated from it by picric acid, by alcoholic mercuric chloride, and as the chloroaurate. Its solubilities in alcohol and water resembled those of most peptides. It could best be purified as the copper salt, of which these workers obtained 8.4 g. from 5.7 kg. of fresh goose muscle. Color tests for histidine, tyrosine, tryptophan, and arginine, as well as a biuret test, were negative. The ninhydrin reaction was positive.

In the same year Linneweh, Keil, and Hoppe-Seyler (75) solved most of the problem of the structure of anserine by means of several experiments and some intuition. The reaction with nitrous acid indicated that one of the four nitrogens was present in a primary amino group. Failure of a solution of the material to decolorize permanganate eliminated the possibility of an aliphatic double bond. Oxidation with chromic acid, chlorine water, permanganate, nitric acid, or hydrogen peroxide, reduction with hydriodic acid, and dry distillation all failed to yield further clues. These investigators therefore resorted to a procedure which had been adapted by Jowett (64e) to pilocarpine, i.e., heating with soda lime in a stream of hydrogen. As a result of this treatment it was possible to isolate 1,5-dimethylimidazole as the chloroaurate, possessing the properties recorded by Jowett for this compound.

This reaction established the presence of an imidazole ring and the locus of the —NCH$_3$ group, and also diminished the number of possible points of attachment of the rest of the molecule. These facts further checked the previous notion that anserine was simply monomethylated carnosine with similar properties. The Pauly diazo color test for the imidazole nucleus, which was positive in the case of carnosine, was negative for anserine. This diazo color evidently, then, required an unsubstituted ring —NH— for its appearance, in agreement with observations of Burian (24).

With the above information as a background it was possible to continue in the same fashion employed for carnosine, as described in the section on that compound. Hydrolysis with barium hydroxide solution gave dl-methylhistidine, separated as the phosphotungstate and isolated and identified as the picrolonate and nitrate. β-Alanine was also isolated from the phosphotungstate filtrate, as the naphthylurea, and it checked in nitrogen content and melting point with a synthetic preparation.

The order of attachment of the two amino acids was not settled by the above work, but the authors suggested that the same order known to exist in carnosine was likely. The validity of this surmise was substantiated by Keil (68a), who employed the device of condensing the peptide with trinitrotoluene (17) and hydrolyzing the resultant compound with dilute sulfuric acid. β-(Dinitrotoluyl)-alanine was isolated.

Keil synthesized both the 1,4- and 1,5-dimethylimidazoles and separated them by the method of Pyman (87f). The chloroaurate of the dimethylimidazole from anserine had a melting point of 224°C., and a mixed melting point with 1,5-dimethylimidazole chloroaurate of 224°C. The structure of anserine was therefore established as
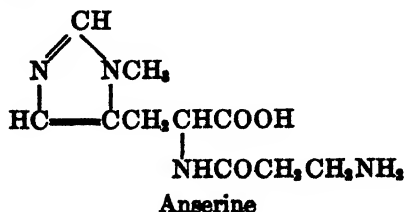
Anserine

Keil (68b) subsequently attempted to synthesize anserine by methylation of carnosine with dimethyl sulfate in soda solution, but a polymethyl product resulted. The partial synthesis of anserine was accomplished by Behrens and du Vigneaud (20), who employed a supply of 1-N-methylhistidine furnished by Ackermann. This compound was converted to the β-alanyl peptide by the method used for carnosine by Sifferd and du Vigneaud (94). The product was identical with natural anserine.

An excellent review on the chemistry and physiology of carnosine and anserine has been published by du Vigneaud and Behrens (100). Anserine has, since 1929, been found in the muscles of many species (113). The possible importance of this compound and of carnosine as natural buffers in muscle systems has been suggested by Smith (95).

B. Carnosine

Carnosine, one of the so-called muscle extractives, was first isolated from "Liebig's meat extract" as the phosphotungstate, silver salt, and nitrate by Gulewitsch and Amiradzibi in 1900 (47). The nitrate was found to exhibit optical activity: $[\alpha]_D^{20} = +22.3°$. A melting range of 211–212°C. was recorded. Analysis of the nitrate and silver salts in both cases corresponded to an empirical formula of $C_9H_{14}N_4O_3$ for the carnosine base. In 1906, Gulewitsch (46a) showed that carnosine was identical with Kutscher's base (74a) "ignotin", as shown by its melting point and the mixed melting point of the nitrates.

The similarity in behavior of carnosine and arginine first suggested to Gulewitsch that the new compound contained a guanidine group. In order to check his belief, the compound was hydrolyzed with barium hydroxide solution, but none of the expected urea was obtained. Instead, there was isolated a base which precipitated with silver nitrate and barium hydroxide. When the argentous precipitate was decomposed with hydrogen sulfide, a base was liberated, the analysis and decomposition point of which corresponded to those of histidine. Its precipitant properties with phosphotungstic acid and with mercuric chloride also agreed with the properties of histidine. From the equation

$$C_9H_{14}N_4O_3 + H_2O = C_6H_9N_3O_2 + C_3H_7NO_2 \text{ (not isolated)}$$

Gulewitsch concluded that the other product was probably alanine.

Subsequently (46b) the hydrolysis was repeated. On this occasion the histidine was completely removed and the residue was treated with α-naphthyl isocyanate. Analysis of the product again indicated $C_3H_7NO_2$. The melting point of the urea was 230–232°C., whereas 198°C. was found to be the melting point for the dl-α-alanine derivative.

Gulewitsch therefore concluded that the compound was β-alanine. This substance was therefore prepared from β-iodopropionic acid and converted into the naphthylureide. The melting point of this compound was 231–233°C. These experiments constituted the first record of the existence of β-alanine in nature.

The constitution of carnosine was thus shown to be either β-alanylhistidine or histidyl-β-alanine. Its structure was unequivocally settled in 1918 by two groups of workers (17, 19).

One of the groups, Baumann and Ingvaldsen (19), first deaminized the carnosine with nitrous acid until 98 per cent of the amino nitrogen had disappeared. From the solution a 70 per cent yield of histidine was isolated, indicating that carnosine is β-alanylhistidine. Carnosine was then synthesized by the following reactions:

$$\text{ICH}_2\text{CH}_2\text{COCl} + \text{Histidine} \xrightarrow{\text{Ba(OH)}_2} \underset{\underset{\text{COOH}}{|}}{\text{ICH}_2\text{CH}_2\text{CONHCHCH}_2\text{Im}^{\,3\,\cdot}}$$

$$\downarrow \text{NH}_3$$

$$\underset{\underset{\text{COOH}}{|}}{\text{NH}_2\text{CH}_2\text{CH}_2\text{CONHCHCH}_2}\text{C}\underset{\underset{\diagdown\text{CH}\diagup}{\text{N}\quad\text{NH}}}{=\!=\!=}\text{CH}$$
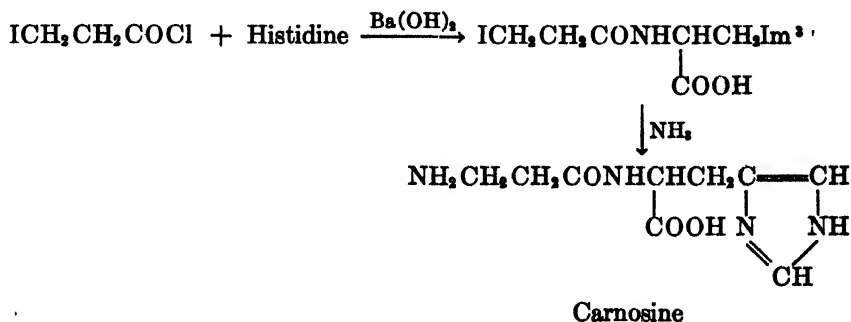
Carnosine

Three grams of carnosine of melting point 250–251°C. was obtained.

Barger (17) reported that he and Ewins also deaminized carnosine and came to the conclusion that the peptide was β-alanylhistidine, but not with certainty, because no pure products were isolated. With Tutin, Barger introduced a new reaction of value in this type of structure determination. These workers found that β- and γ-trinitrotoluenes condense with amino acids, when dilute alcoholic solutions of the substances are boiled, with the liberation of nitrous acid. The reaction occurs with primary amino groups only. γ-Trinitrotoluene condensed with carnosine as follows:
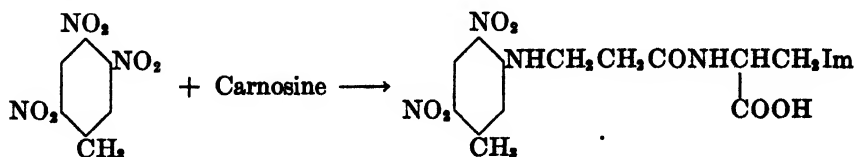
When this substance was hydrolyzed, histidine was isolated.

An attempt to synthesize the peptide from β-chloropropionylhistidine with ammonia did not yield the desired peptide. Histidine methyl ester and β-nitropropionyl chloride were then coupled and reduced by stannous chloride and acid. A small amount of the copper salt of the hydrolyzed reduction product was obtained, but perfection of the method was abandoned, owing to the prior publication of Baumann and Ingvaldsen's process.

A yield ten times as great as that of the early syntheses was recorded by

³ Im = imidazolyl.

Sifferd and du Vigneaud in 1935 (94), employing the Curtius and Bergmann reactions:

$$RCOOH^4 \longrightarrow RCONHNH_2 \longrightarrow RCON_3 \longrightarrow$$

$$RCONHCHCH_2Im \longrightarrow RCONHCHCH_2Im$$
$$\;\;\;\;\;\;\;\;\;\;\;|\qquad\qquad\qquad\qquad\qquad\; |$$
$$\;\;\;\;COOCH_3 \qquad\qquad\qquad\;\;\;\; COOH$$
$$\qquad\qquad\qquad\qquad\qquad\qquad\qquad |$$
$$\qquad\qquad\qquad\qquad\qquad\qquad Carnosine$$
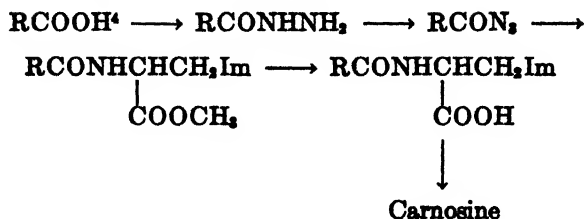
The over-all yield from histidine was 65 per cent.

Methyl histidinate was successfully condensed with β-alanyl chloride in another method (55). Abderhalden (1) also successfully concluded Barger's attempted synthesis, by employing the methyl ester of histidine.

du Vigneaud and Hunt (101) prepared d-carnosine and found that this gave no blood pressure lowering in twenty times the dose adequate to give a pronounced effect with l-carnosine. The short-lived depressor effect of l-carnosine is not of pharmacological importance, although it may be important physiologically.

C. Ergothioneine

Ergothioneine (thioneine, thiasine) derived its name from its original isolation from an alcoholic extract of ergot by Tanret (98). It has been isolated from other sources, such as mammalian blood (61). Tanret found the substance to be optically active with $[\alpha]_D = +110°$ (no temperature was given). The compound proved to be a weak base and formed salts with mineral acids and mercuric chloride. It had the empirical formula $C_9H_{15}O_2N_3S$. Practically all of the structural work published on ergothioneine is contained in the paper of Barger and Ewins (16). From the facts that it formed a silver precipitate as histidine does, and had a large nitrogen content these workers suspected the presence of an imidazole ring. The carbon and hydrogen content also suggested a betaine group to them. Confirmation of the first guess was furnished by the red color obtained with p-diazobenzenesulfonic acid, a color reaction typical of imidazoles (61).

Heating with concentrated potash cleaved ergothioneine to trimethylamine and a yellow acid having the composition shown by the formula $C_6H_6O_2N_3S$.

$$
\begin{array}{ccc}
SH & & SH \\
| & & | \\
C & & C \\
HN \diagup \diagdown N & \longrightarrow & HN \diagup \diagdown N \qquad + (CH_3)_3N \\
| \qquad\quad | & & | \qquad\quad | \\
HC{=\!=}CCH_2CHCOO^- & & HC{=\!=}CCH{=}CHCOOH \\
\qquad\qquad | & & \\
\qquad\quad N^+(CH_3)_3 & &
\end{array}
$$

Ergothioneine
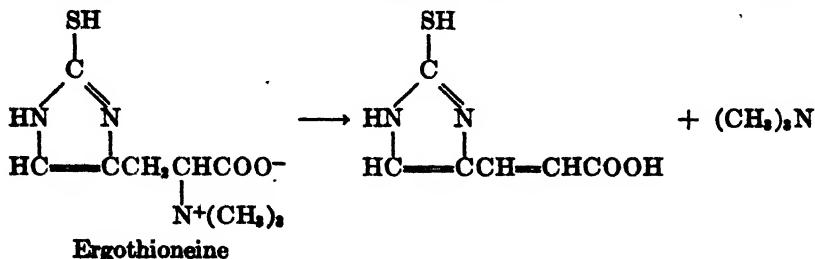
[4] $R = C_6H_5CH_2OCONHCH_2CH_2{-}.$

When the sulfur of the acid was oxidized away with nitric acid and the resultant compound was reduced with sodium and ethanol, there resulted a substance which, by melting point and mixed melting point, was shown to be identical with an authentic specimen of β-imidazolylpropionic acid.

Oxidation of the original compound with iodine gave a disulfide. The substance thus showed a similarity in reaction to cysteine, in contrast to its stability toward hot alkali, which would not obtain for cysteine. From these results Barger and Ewins concluded that the sulfur was present in thiolimidazole form, although they did not rule out as possible an attachment of sulfur to the beta carbon atom.

The position of the sulfur in the ring was confirmed synthetically twenty-two years later by Akabori. Akabori (9) prepared thiolimidazolylpropionic acid from glutamic acid, by a ring closure known to give thiolimidazoles; the same compound was obtained by reduction of Barger and Ewins' thiolimidazolyl-acrylic acid with sodium amalgam.

$$C_2H_5OCOCHCH_2CH_2COOC_2H_5 \xrightarrow{\text{Na-Hg}} CHOCHCH_2CH_2COOH \xrightarrow{\text{HSCN}}$$
$$\underset{NH_2 \cdot HCl}{\qquad\qquad\mid\qquad\qquad\qquad}\qquad\qquad \underset{NH_2 \cdot HCl}{\mid\qquad\qquad}$$

$$HC{=\!=\!=}CCH_2CH_2COOH$$
$$\underset{N\qquad NH}{\mid\qquad\mid}$$
$$\underset{C}{\diagdown\;\diagup}$$
$$\mid$$
$$SH$$
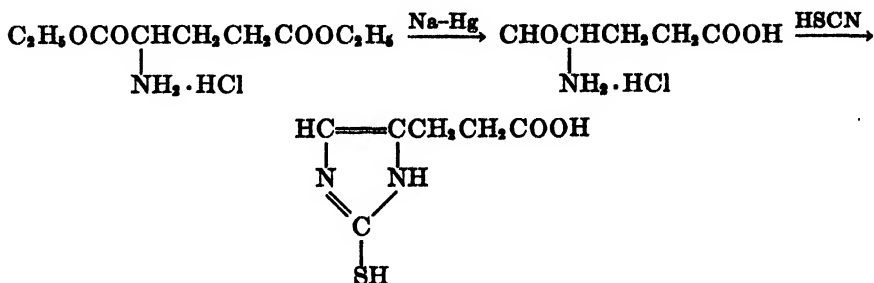
Although attempts to synthesize ergothioneine have been made, this goal has not yet been attained. Jackson and Marvel (62) attempted the preparation of a possibly useful intermediate from 2-thiol-4(or 5)-hydroxymethylimidazole. Experiments designed to convert the hydroxyl group to chloride by thionyl chloride and by hydrochloric acid were, however, unsuccessful because of polymer formation.

At about the same time several attempts at the same preparation were recorded by Harington and Overhoff (53). Their paper also includes a critical analysis of the synthetic problem and the various possible approaches. These investigators concluded that the most likely mode of synthesis will involve the action of trimethylamine on an appropriate halogen compound. The problem of synthesis therefore remains to be solved. The physiological importance of ergothioneine, if any, has yet to be established also.

Ergothioneine is one of the non-sugar-reducing substances in blood and its value may be related to this fact (18). Extensive tests emphasizing its negative pharmacological action have been reported by Tainter (97).

D. Histamine

This physiologically important amine is probably the best known of the imidazole group. Before it was recognized as a naturally occurring substance,

histamine was prepared (70, 112) by Windaus and Knoop as part of a program of syntheses of imidazoles (110). The process was built around a Curtius degradation:

$$CH_3COCH_2CH_2COOH \longrightarrow CH_2BrCOCHBrCH_2COOH \longrightarrow$$

$$CHOCOCH_2CH_2COOH \xrightarrow[\text{HCHO}]{NH_3} ImCH_2CH_2COOH^\flat \xrightarrow[\text{HCl}]{C_2H_5OH}$$

$$ImCH_2CH_2COOC_2H_5 \xrightarrow{NH_2NH_2} ImCH_2CH_2CONHNH_2 \xrightarrow{HNO_2}$$

$$ImCH_2CH_2CON_3 \xrightarrow{HCl} ImCH_2CH_2NH_2$$
$$\text{Histamine}$$
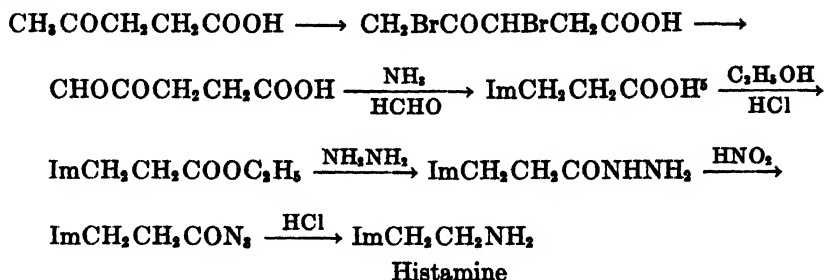
In 1910, Barger and Dale (15) and Kutscher (74b) simultaneously announced the discovery of the amine in extracts of ergot. In this same year, Ackermann (4a) recorded the enzymic decarboxylation of histidine to histamine. Histamine was thus the second proteinogenous amine to be isolated, following tyramine.

Another synthesis of histamine, by Pyman (87a), followed soon after this discovery. Diaminoacetone was synthesized by the method of Kalischer (65) and converted in the usual fashion to the thiolimidazole.

$$\begin{array}{cccc} CH_2COOH & CH_2COOH & CH=NOH & CH_2NH_2 \\ | & | & | & | \\ HOCCOOH & CO & CO & CO \\ | & | & | & | \\ CH_2COOH & CH_2COOH & CH=NOH & CH_2NH_2 \end{array}$$

$$\underset{NH_2CH_2C}{\overset{HC-NH}{\underset{\big\|}{\big\|}}}\underset{N}{\diagdown}CSH \xrightarrow{HNO_2} ImCH_2OH \xrightarrow{PCl_5} ImCH_2Cl \xrightarrow{NaCN}$$

$$ImCH_2CN \xrightarrow{Na + C_2H_5OH} \text{Histamine}$$
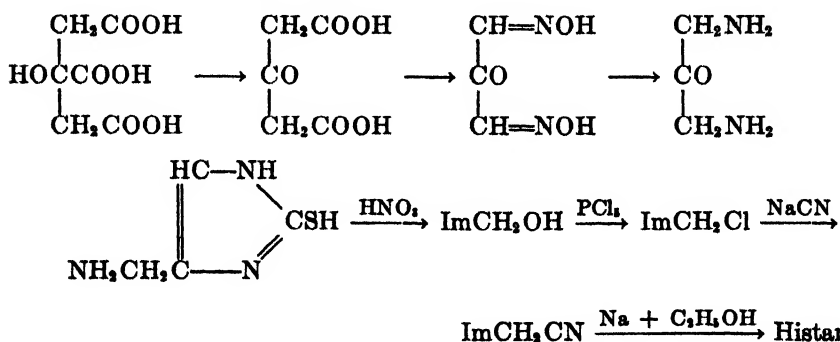
During the oxidation of the thiolimidazole, nitrous acid is formed, and converts the terminal amino group to hydroxyl. Yields were all above 60 per cent, except in the last step which gave 29 per cent conversion to histamine. Imidazolylacetic acid was also isolated by Pyman, in 35 per cent yield from the nitrile.

The Pyman–Kalischer synthesis has been improved by Koessler and Hanke (71). The intermediate hydroxymethylimidazole may be directly obtained from fructose (28, 104). An inexpensive but useful form of fructose for this reaction is honey freed of glucose (38).

Another synthesis of histamine by Pyman (23) starts with $NH_2CH_2CH_2$-$COCH_2NH_2$. This is condensed to the thiolimidazole with thiocyanic acid, and oxidized to histamine by ferric ion. Yet another synthesis by Pyman (41)

$^\flat$ Im = imidazolyl.

converts hydroxyethylimidazole (histidol) to the chloride, and thence to the amine (80 per cent) with alcoholic ammonia.

$$
\begin{array}{c}
\text{HC—NH} \\
\diagdown \\
\text{C}_6\text{H}_5\text{OCH}_2\text{CH}_2\overset{\|}{\text{C}}\text{—N}
\end{array}\diagup\text{CSH} \rightarrow
\begin{array}{c}
\text{HC—NH} \\
\| \quad \diagdown \\
\text{C}_6\text{H}_5\text{OCH}_2\text{CH}_2\text{C—N}
\end{array}\diagup\text{CH} \rightarrow \text{Histidol} \quad (1)
$$

(10 per cent yield)

$$
\begin{array}{c}
\text{CHNH}_2\text{CO} \\
| \qquad \diagdown \\
| \qquad \quad \text{O} \longrightarrow \\
\text{CH}_2\text{CH}_2\diagup
\end{array}
\qquad
\begin{array}{c}
\text{HC—NH} \\
\diagdown \\
\text{HOCH}_2\text{CH}_2\overset{\|}{\text{C}}\text{—N}
\end{array}\diagup\text{CSH} \longrightarrow \text{Histidol} \quad (2)
$$

(30 per cent yield)
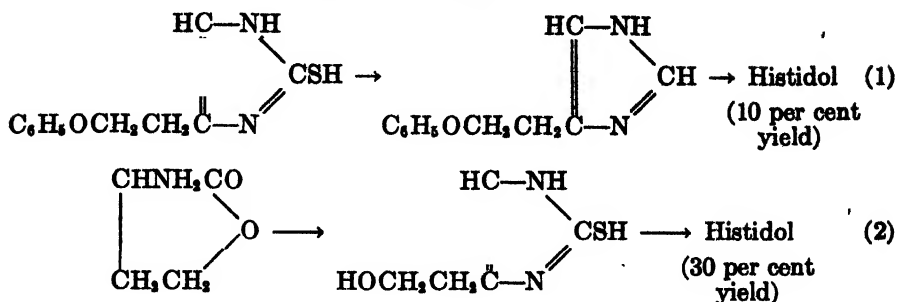
Besides these syntheses, Ewins and Pyman (36) developed the chemical decarboxylation of histidine to histamine. This involved reaction periods of a few hours, instead of the weeks employed in Ackermann's bacterial process. This method is the principal one used for the commercial preparation of histamine. Ewins and Pyman found that heating with 20 per cent sulfuric acid, 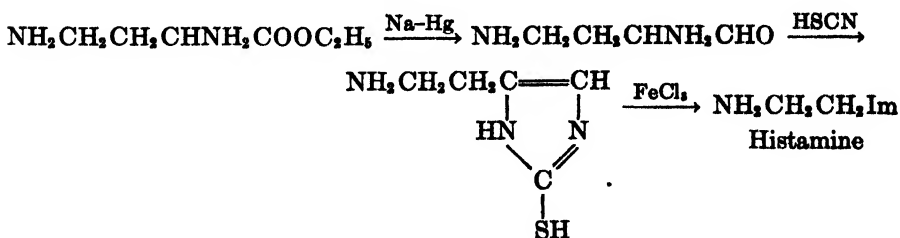concentrated hydrochloric acid, or potassium acid sulfate gave no decarboxylation in 3 hr. at 240°C. At 265–270°C., however, yields up to 25 per cent were obtained. Histidine, benzoylated on the α-amino group, could be heated at 240°C. in a vacuum, alone, and the resultant benzoylhistamine hydrolyzed to give yields of 10 to 20 per cent.

The most recent synthesis of histamine was reported by Akabori and Numano (11c). Glutamic acid was converted in six steps to α, γ-diaminobutyric acid (also prepared (8) by the action of hydrazoic acid on glutamic acid), from which the synthesis proceeded as follows:

$$
\text{NH}_2\text{CH}_2\text{CH}_2\text{CHNH}_2\text{COOC}_2\text{H}_5 \xrightarrow{\text{Na–Hg}} \text{NH}_2\text{CH}_2\text{CH}_2\text{CHNH}_2\text{CHO} \xrightarrow{\text{HSCN}}
$$

$$
\begin{array}{c}
\text{NH}_2\text{CH}_2\text{CH}_2\text{C}\!=\!\!=\!\!\text{CH} \\
\text{HN} \qquad \text{N} \\
\diagdown \qquad \diagup \\
\text{C} \\
| \\
\text{SH}
\end{array}
\xrightarrow{\text{FeCl}_3} \begin{array}{c}\text{NH}_2\text{CH}_2\text{CH}_2\text{Im} \\ \text{Histamine}\end{array}
$$

The medical utility of histamine includes its use as a gastric stimulant (it is probably a natural gastric hormone (90)), and in ointments for the treatment of rheumatism. An excellent review of the physiological literature to 1931 has been published by Best and McHenry (21a). Histamine is believed to be liberated as part of the mechanism of allergic manifestations in shock, urticaria, asthma, sneezing, etc. For such maladies it has been recommended as a desensitizing agent (37a, 105).

In a recent paper, Kapeller-Adler (66) describes an isolation of histamine. The base is finally separated as the diflavianate, and a few milligrams are re-

coverable. By this method it was possible to demonstrate that, although histidine is excreted by normal pregnant women, histamine, instead, is excreted by those suffering from toxemia.

E. Histidine

Kossel (72) is credited with the original isolation of histidine, from the protamine sturine. Kossel gave the base its present name. The compound was isolated by sulfuric acid hydrolysis and separation as the mercury salt. After removal of mercury, the base was neutralized with hydrochloric acid, and the hydrochloride was isolated. Analysis indicated either $C_{12}H_{20}N_6O_4 \cdot 2HCl + 2H_2O$ or $C_6H_9N_3O_2 \cdot HCl + H_2O$. A small amount of histidine was prepared by removing chloride ion with silver and precipitating from the concentrated aqueous solution with alcohol and ether. The amount of material obtained permitted three analyses, two of which corresponded most closely to the C_6 formula. On the other hand, the boiling-point elevation in phenol indicated a molecular weight of 296, whereas the C_{12} formula requires 312.
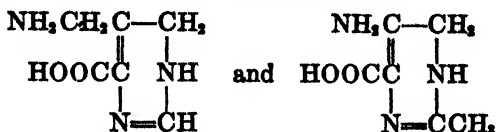
In the same number of "Hoppe-Seyler" (56), Hedin reported further on the chemistry of histidine isolated from blood serum and from casein. The material was prepared from the arginine filtrate with silver, giving $C_6H_{12}N_3O_3Cl$. The base analyzed as $C_6H_9N_3O_2$. A determination of molecular weight by freezing-point lowering, more dependable than Kossel's ebullioscopic method, indicated 155.4 as against a theoretical value of 155.1. The C_6 formula was thus firmly established.

Hedin found that histidine could be precipitated from its aqueous solution by careful addition of ammonia. This precipitate dissolved in excess ammonia. Attempts to obtain a crystalline sulfate or nitrate were unsuccessful. Identity of the substance with Kossel's histidine was proven by crystallographic comparison. Kossel and Kutscher reported later (73), in contrast to Hedin, that natural histidine is optically active: $[\alpha]_D = -39.7°$. Kossel and Kutscher showed that histidine dihydrochloride, melting point 231–233°C., could be obtained from the monohydrochloride by evaporation with hydrochloric acid.

Herzog (57) reported several chemical tests run on a sample of histidine. The tests chosen indicated that Herzog was unaware of the type of structure present in his compound. He noted a positive biuret reaction, which was probably due to the presence of peptide impurities. Methoxyl and methylimide tests were negative. It was reported that hydroxylamine hydrochloride reacted with histidine to give a crystalline substance. Oxidation with barium permanganate in neutral solution evolved hydrocyanic acid. Histidine also reacted as a saturated substance when tested with bromine in acetic acid. From these tests, Herzog concluded that the substance was neither dimethyl malonylguanide nor malonylguanide, which conclusion was correct as far as it went.
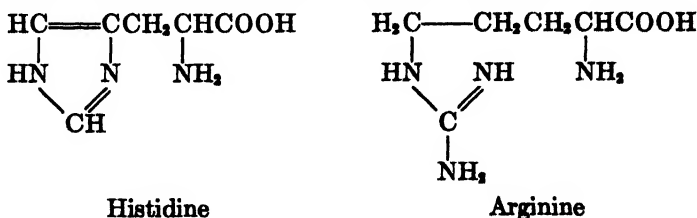
Fraenkel (40a) heated histidinium chloride above its melting point and found that carbon dioxide was evolved. This reaction indicated the presence of a carboxyl group, and histidine could be formulated as $C_5H_8N_3COOH$. Sodium

hypobromite was found to remove one nitrogen; therefore one amino group was present. Fraenkel, however, reported a positive Wiedel reaction, which incorrectly led to the suggestion of the two pyrimidine structures

$$
\begin{array}{cc}
\text{NH}_2\text{CH}_2\text{C—CH}_2 & \text{NH}_2\text{C—CH}_3 \\
\parallel \quad | & \parallel \quad | \\
\text{HOOCC} \quad \text{NH} \quad \text{and} & \text{HOOCC} \quad \text{NH} \\
| \quad\quad | & | \quad\quad | \\
\text{N=CH} & \text{N=CCH}_3
\end{array}
$$

By a critical review of the published observations and by means of a few well-chosen experiments, Pauly (82) arrived at the now-accepted structure, of histidine. He failed to get a definite compound from histidine by the action of benzoyl chloride and alkali, but succeeded with benzenesulfonyl chloride. Two molecules reacted for each molecule of histidine. Since one nitrogen had already been shown to be a primary amino nitrogen, there was thus evidently a secondary amino nitrogen also, and the third was correctly concluded to be tertiary nitrogen. From the analysis, Pauly concluded that there must be two double bonds or a triple bond. Only one could be between nitrogen and carbon, since one nitrogen bore a hydrogen atom. If a =C=NH group were present, barium hydroxide treatment, in contrast to the experimental finding, would hydrolyze it. The other double bond must be between two carbon atoms. Stability to acid permanganate indicated that the double bonds must be in the ring.

Two two-nitrogen rings were known at the time—pyrazole and imidazole. Pauly considered that the former did not merit consideration as a physiological component. Because of the close physiological and chemical similarity to arginine, Pauly suggested the correct formula for histidine:

$$
\begin{array}{cc}
\text{HC=CCH}_2\text{CHCOOH} & \text{H}_2\text{C—CH}_2\text{CH}_2\text{CHCOOH} \\
| \quad\quad | \quad\quad | & | \quad\quad | \quad\quad\quad | \\
\text{HN} \quad \text{N} \quad \text{NH}_2 & \text{HN} \quad \text{NH} \quad\quad \text{NH}_2 \\
\searrow \quad \nearrow & \searrow \quad \swarrow \\
\text{CH} & \text{C} \\
& | \\
& \text{NH}_2
\end{array}
$$

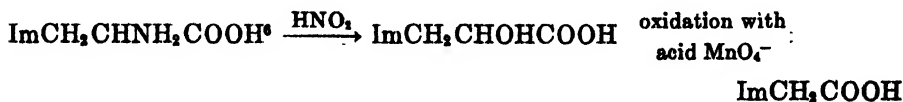$$\text{Histidine} \qquad\qquad \text{Arginine}$$

The imidazole authorities, Knoop and Windaus (70), reported experiments designed to settle whether the histidine ring was a derived pyrimidine structure of the type suggested by Fraenkel, or was Pauly's imidazole. Knoop and Windaus treated histidine with sodium and alcohol, without change. A reaction would not be expected with an imidazole, whereas one would be with a pyrimidine (26). Further, by reducing Fraenkel's desaminohistidine with hydriodic acid and phosphorus, they obtained an acid of melting point 208–209°C. This substance was shown to be identical with imidazolylpropionic acid, an intermediate in their histamine synthesis described above.

Fraenkel, however, refused to accept the accumulated evidence for the imidazole structure. In a short paper (40c) he pointed out that pyrimidine

derivatives with no oxygen in the ring give a color with diazobenzenesulfonic acid as does histidine.   A more logical argument was the statement that the Bamberger reaction (fission of the imidazole ring by acid chloride in alkali) did not occur with histidine when it was treated with benzenesulfonyl chloride. This argument is of little significance however, since, even to the present date, the specificity of the Bamberger reaction has not been thoroughly elucidated, and it is clear that the reaction is not a general one.

Knoop (69) also settled the position of the amino group by the following reaction:

$$ImCH_2CHNH_2COOH^* \xrightarrow{HNO_2} ImCH_2CHOHCOOH \xrightarrow[\text{acid } MnO_4^-]{\text{oxidation with}}$$

$$ImCH_2COOH$$

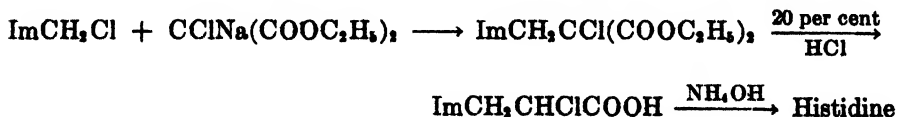An acid of the correct analysis for imidazolylacetic acid was obtained.

The synthesis of histidine did not occasion as many false starts as did the determination of its structure, but it also was not without an unfruitful attempt. Gerngross (42a) first attempted a synthesis from methylimidazole as follows:

$$+ CCl_3CHO \longrightarrow ImCH_2CHOHCCl_3 \longrightarrow$$

$$ImCH_2CHOHCOOH \longrightarrow ImCH_2CH(NH_2)COOH$$
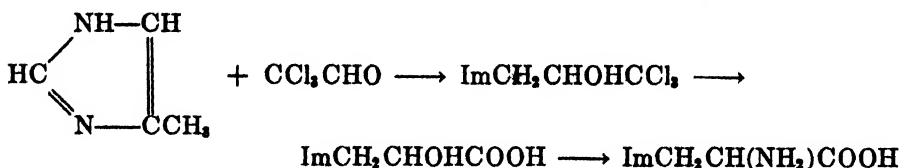
Gerngross thought the first step went as expected, but it was later shown that condensation occurred on the unsubstituted 4(or 5)-carbon atom (106).   This was established by hydriodic acid reduction of the formaldehyde condensation product to dimethylimidazole:

Dimethylimidazole
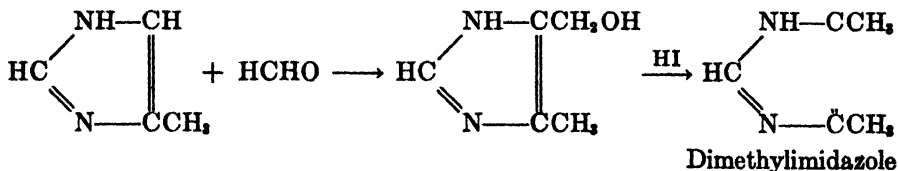
The only recorded syntheses of histidine are those due to Pyman (87b, 87e). Pyman employed imidazolylmethyl chloride, an intermediate in his histamine synthesis.   He reacted this with the novel reagent, sodiochloromalonic ester:

$$ImCH_2Cl + CClNa(COOC_2H_5)_2 \longrightarrow ImCH_2CCl(COOC_2H_5)_2 \xrightarrow[\text{HCl}]{20 \text{ per cent}}$$

$$ImCH_2CHClCOOH \xrightarrow{NH_4OH} \text{Histidine}$$

* Im = imidazolyl.

In Pyman's later preparation an Erlenmeyer synthesis was employed:

$$ImCH_2OH \xrightarrow{HNO_2} ImCHO \xrightarrow[C_6H_5CONHCH_2COOH]{(CH_3CO)_2O + CH_3COONa}$$
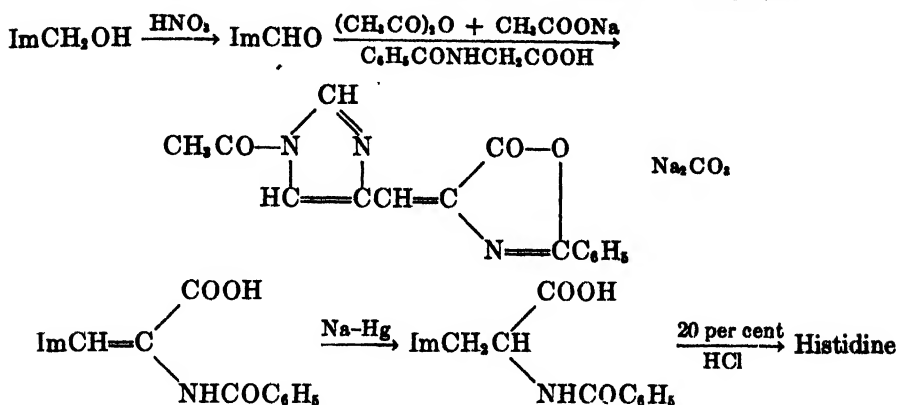
Abderhalden and Weil (3) worked out a resolution of histidine with d-tartaric acid.

Histidine is an "essential" amino acid (7). It has achieved some recognition as a medicament in the treatment of ulcers. Commercially it is made by isolation from blood paste and from other protein sources. The uncoupled imidazole radical of histidine contributes to the basic properties of proteins. A large part of the ability of the proteins to form azo dyes can be attributed to histidine also. That it is the 1-nitrogen atom and not the 4- or 5-carbon atom which couples was demonstrated by Burian (24), who found that N-methylimidazole did not react, whereas N-unsubstituted imidazoles, including purines, did.

F. Pilocarpine and related alkaloids

Several alkaloids have been isolated from the leaves of *Pilocarpus jaborandi*. These include pilocarpine (the one known to medicine), isopilocarpine, pilocarpidine, and pilosine.

Pilocarpine was discovered independently by Hardy (51) and Gerrard (43) in 1875. Harnack and Meyer (54) established the empirical formula of $C_{11}H_{16}O_2N_2$. Hardy and Calmels (50) presented a volume of evidence that the alkaloid was a derivative of β-pyridyllactic acid and trimethylamine. This was shown by others, such as Merck (77), to be an incorrect formulation.

Elucidation of the structure of pilocarpine was the result of the labors of Jowett (64a, c, d, e, f) and of Pinner and Schwarz (83). Jowett first found that pilocarpine was converted to isopilocarpine by heat. It was convenient to conduct the structural studies on the latter isomer. By oxidation with permanganate, Jowett obtained a new acid, $C_7H_{10}O_4$, which he named pilopic acid. Titration of pilopic acid showed it to be lactonic, and since further oxidation resulted in butyric acid, the formula C_2H_5CH—$CHCOOH$ was suggested.

$$COOCH_3$$

The silver and barium salts, the ester, and the diamide of the dicarboxylic acid were prepared. The homolog, homopilopic acid, C_2H_5CH—$CHCH_2COOH$,

$$\underset{\overset{|}{COOCH_3}}{}$$

was also obtained by oxidation of isopilocarpine. Alkaline fusion of the latter led to the compound $C_2H_5CH(COOH)CH(COOH)CH_2COOH$, previously known.

The suggestion that the nitrogenous moiety was an imidazole came from Pinner and Schwarz. These investigators found a small quantity of methylurea after oxidizing the alkaloid. From this information, from the fact that substitution rather than addition of active reagents occurred, and with the empirical formula as a background, the imidazole structure was deduced.

To confirm this deduction partially, a test developed by Rung and Behrend (89) was applied. The original imidazole did not evolve an amine on alkaline treatment, but the ethyl iodide addition product did. From such evidence, the two formulas
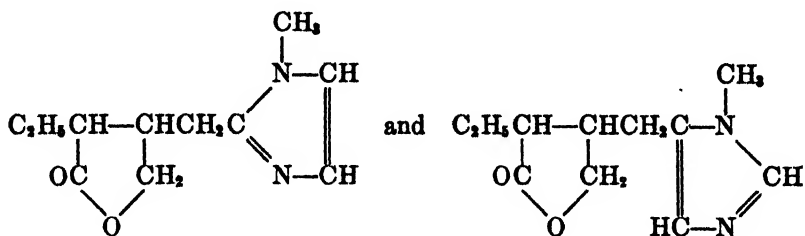
were proposed. The second structure, later shown to be correct, was favored because it was more likely to yield methylurea on oxidation.

Since the above evidence was not conclusive, Jowett studied the products of alkaline pyrogenesis of isopilocarpine. He found
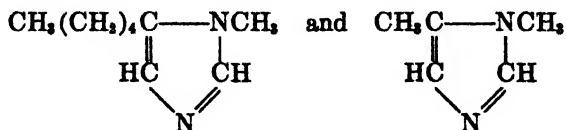
The latter was established by comparison with the synthetic 1,5-dimethylimidazole (64f, 87f).

Although the formula was thus established and Jowett attempted the synthesis by various approaches, it was not until 1933 that a synthesis was announced from Moscow (85, 86, 99).

$$\underset{\underset{C_2H_5OOC}{\displaystyle|}}{C_2H_5}CHCHCOOC_2H_5 \quad \xrightarrow{\text{distillation}} \quad RCOOC_2H_5{}^7 \xrightarrow{HCl}$$

<div align="center">

Pilopic ester
(Isopilopic ester)

</div>

$$RCOOH \longrightarrow RCOCl \xrightarrow{CH_2N_2} RCOCHN_2 \xrightarrow[H_2O]{Ag_2O}$$

$$RCH_2COOH \xrightarrow{SOCl_2} RCH_2COCl \xrightarrow{CH_2N_2} RCH_2COCH_2Cl \longrightarrow$$

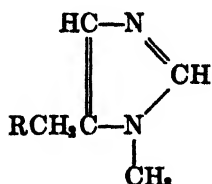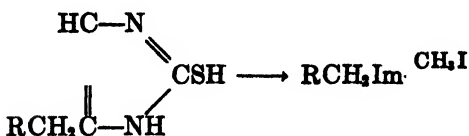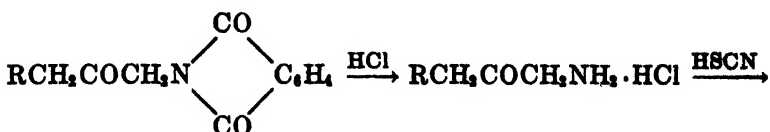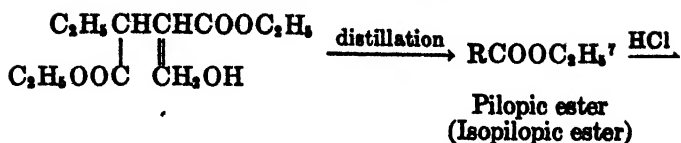$$RCH_2COCH_2N\underset{CO}{\overset{CO}{\diamondsuit}}C_6H_4 \xrightarrow{HCl} RCH_2COCH_2NH_2 \cdot HCl \xrightarrow{HSCN}$$

$$RCH_2Im \cdot \xrightarrow{CH_3I}$$

<div align="center">
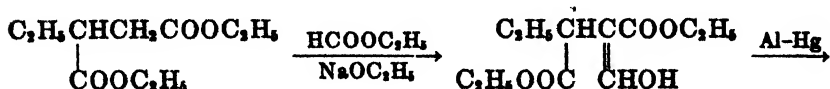
Pilocarpine
(Isopilocarpine)

</div>

There were obtained both pilocarpine and isopilocarpine by the use of stereo-isomeric homopilopic acids separated with strychnine. The yield of pilocarpine nitrate was 29 mg.

Dey (30a) has developed an alternative synthesis for the homopilopic acids. These were converted to the alkaloids as follows:

$$RCH_2COOH \longrightarrow RCH_2COCl \xrightarrow{CH_2ZnI} RCH_2COCH_3 \xrightarrow{C_6H_5CHO}$$

$$RCH_2COCH=CHC_6H_5 \xrightarrow{O_3} RCH_2COCHO \quad \overset{NH_3}{\underset{HCHO}{}}$$

$$RCH_2Im \xrightarrow{CH_3I} \text{Pilocarpine}$$

<div align="center">

(Isopilocarpine)

</div>
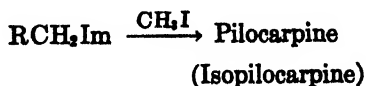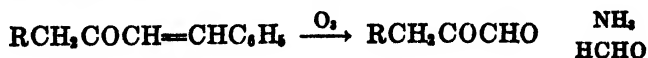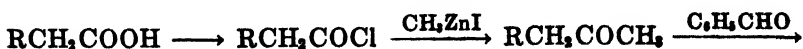
Pilocarpine is widely used in medicine as a diaphoretic and myopic.

$${}^7 R = C_2H_5CH\underset{\underset{O}{\diagdown \diagup}}{\overset{\displaystyle|}{OC}}\underset{\underset{}{}}{\overset{\displaystyle|}{CH}}\underset{CH_3}{}-.$$
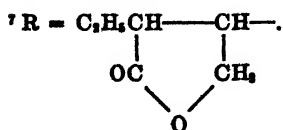
Pilosine (87d) has been decomposed into benzaldehyde and pilosinine. Pilosine is believed to be

$$C_6H_5\,CHOHCH—CHCH_2\,C—N^{CH_3}\quad CH$$
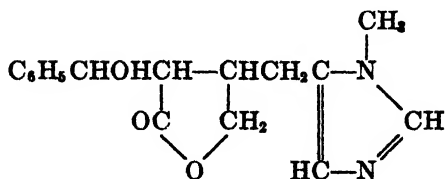
Pilosine possesses to a lesser degree the physiological properties of pilocarpine.

The synthesis of pilosinine has been accomplished (84) starting from succinic ester and following the procedure given above for pilocarpine. In a variant of the synthesis, the imidazole portion of the molecule was built up as follows:

$$H_2C——CHCH_2COOH \qquad H_2C——CHCH_2COCHN_2$$

$$H_2C-\quad CHCH_2COCH_2OCOCH_3 \quad Cu(NH_3)_4{}^+$$
$$HCHO$$

$$H_2C——CHCH_2C-\,-NH \quad CH_3I \quad H_2C——CHCH_2C—N^{CH_3}$$

Pilosinine
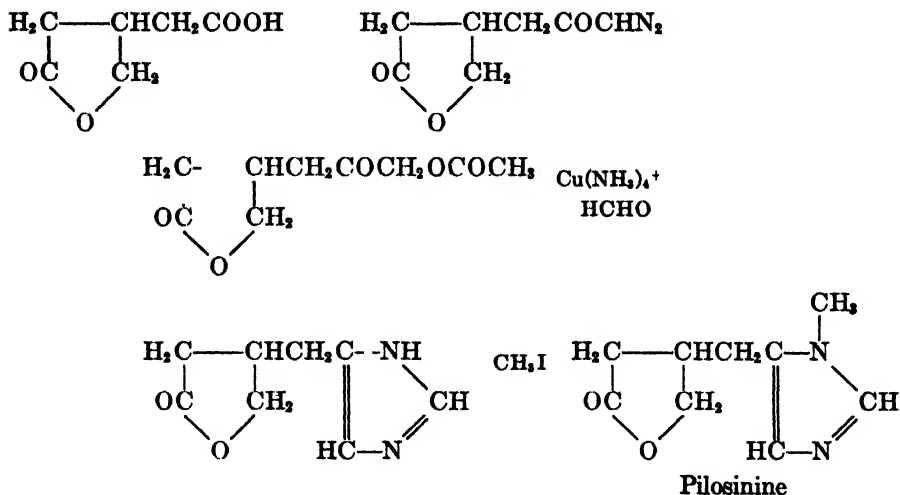
Pilocarpidine, the imino compound corresponding to pilocarpine, has been reported as a jaborandi alkaloid which is found infrequently (64b). Methylation of pilocarpidine (25) yields pilocarpine.

G. 2-Thiolhistidine

The presence of thiolhistidine in protein has not been proved by isolation. In 1928 Hunter (61) discovered that diazotized sulfanilic acid gave a specific purple-red color with the thiolimidazole nucleus when the test was carried out under special conditions. In the same year, Eagles and Vars (31) applied the test to a number of proteins and found that zein gave a strong positive reaction. Since zein contains appreciable amounts of sulfur which cannot be accounted for as cystine, the likelihood that this unexplained sulfur is in thiolhistidine is increased.

Harington and coworkers are credited with two syntheses of this compound.

In the first synthesis (14), histidine serves as an initial material which is converted to a desired intermediate by a Bamberger reaction:
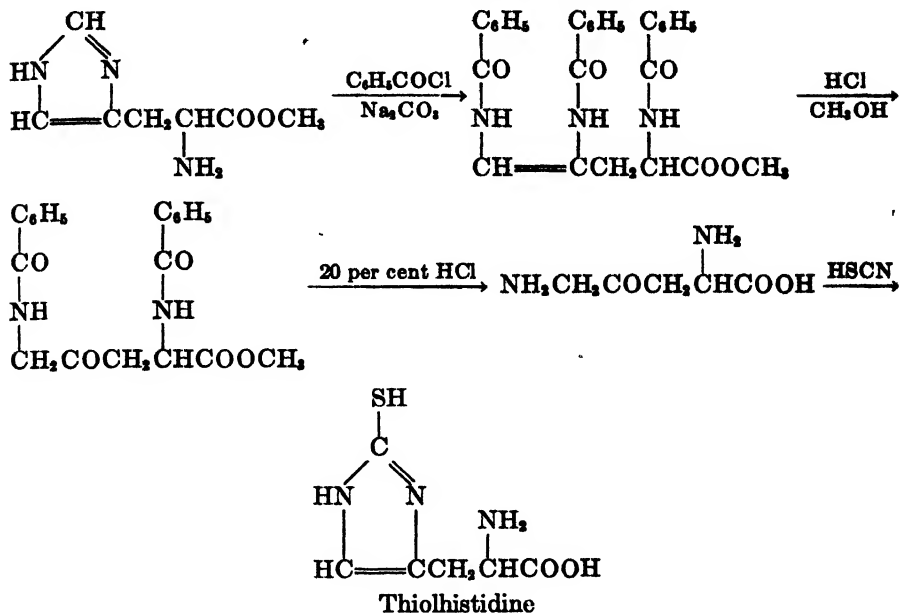
$$\text{Thiolhistidine}$$

The nature of the product was proved by almost quantitative conversion to histidine with ferric sulfate. Both the starting and final products were optically active.

The second synthesis was developed during attempts to prepare ergothioneine (53):
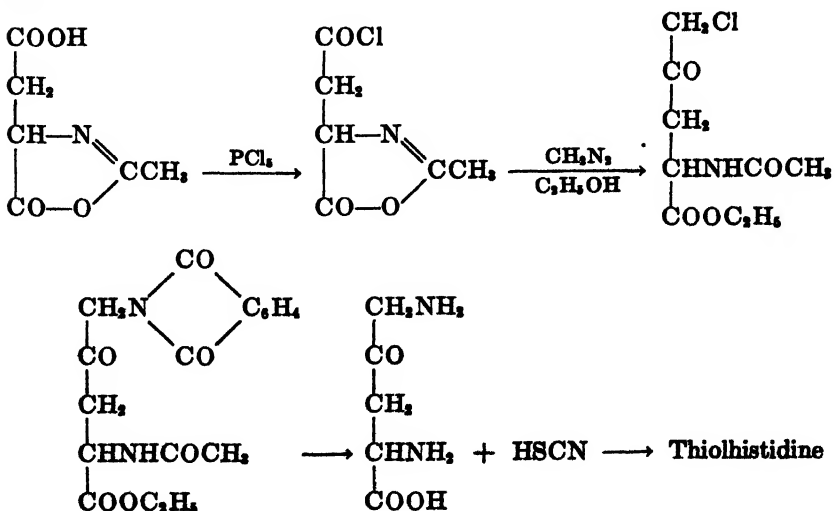
Dey (30b) has also recorded two syntheses, which are similar. His products were racemic. In the first synthesis:

$$RCH_2COCH_2I^* + RCNa(COOC_2H_5)_2 \rightarrow RCH_2COCH_2CR(COOC_2H_5)_2 \xrightarrow{HBr}$$

$$NH_2CH_2COCH_2CH(NH_2)COOH \cdot 2HBr \xrightarrow{HSCN} \text{Thiolhistidine}$$

III. OTHER NATURALLY OCCURRING IMIDAZOLES

A. Dimethylhistamine

Ackermann and coworkers (5) have isolated as the picrate a dimethylhistamine from *Geodia gigas*. The structure was determined by a positive diazo reaction and analysis. Although the structure is probably correct, synthetic confirmation is lacking, and the positions of the methyl groups have not been fixed.

B. Hercynin

Hercynin was discovered in mushrooms (74c) and molds (88, 111). The facts that it gave a Pauly reaction for the imidazole nucleus and that it analyzed as the betaine of histidine led Kutscher to deduce its structure correctly:

$$ImCH_2CHCOO^-$$
$$|$$
$$N^+(CH_3)_3$$

Hercynin

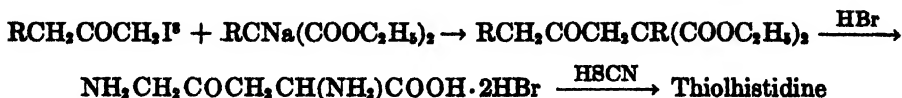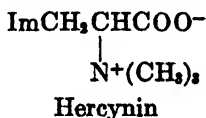The partial synthesis of hercynin was first reported by Barger and Ewins (16), who oxidized ergothioneine with ferric chloride. Another synthesis (35) depends upon the reaction of the reaction product of histidine and nitrous acid with alcoholic trimethylamine. The intermediate was not isolated, but it was undoubtedly imidazolyllactic acid, and the reactivity of the hydroxyl group with trimethylamine is somewhat surprising in an aliphatic side chain.

C. Histidol

Histidol, 4(or 5)-hydroxyethylimidazole, $ImCH_2CH_2OH$, was discovered by Ehrlich (32) as a product of yeast fermentation of histidine. Three syntheses have been recorded (41, 109). The simplest of these involves the treatment of histamine with nitrous acid. Pyman and Garforth (41) synthesized histidol by two methods which use it as an intermediate for histamine (see page 54).

D. Imidazolylglycine

A small amount of imidazolylglycine, $ImCH(NH_2)COOH$, was isolated from normal human urine as the picrolonate, by Engeland (34). The compound was synthesized by Stewart (96) from imidazole aldehyde by the Strecker reaction. The melting point of the picrolonate of Stewart's base was 243°C., 1°C. lower than that reported by Engeland. Since the range of melting points of compounds of this type is not large, however, a mixed melting point with an isolated specimen is to be desired.
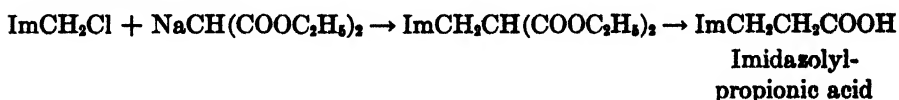
* $R = C_6H_4(CO)_2N-$.

E. Imidazolyllactic acid

Imidazolyllactic acid, $ImCH_2CHOHCOOH$, was found as a bacterial product (59). Hirai obtained it in 11 per cent yield from histidine by the action of *Proteus vulgaris*. Prior to this discovery, two syntheses were recorded. Fraenkel (40b) isolated the compound as a reaction product of histidine hydrochloride and silver nitrite. Pyman prepared it from the chloro analog that he used in the synthesis of histidine (87b). Conversion was brought about by moist silver oxide.

F. Imidazolylpropionic acid

This compound represents another bacterial conversion product of histidine (4b). Prior to its discovery as a natural product, Knoop and Windaus (70) prepared it by the hydriodic acid reduction of imidazolyllactic acid, and by the condensation of glyoxylpropionic acid with ammonia and formaldehyde as on page 54. The compound was also prepared by Pyman (87b) from (imidazolylmethyl)malonic acid.

$$ImCH_2Cl + NaCH(COOC_2H_5)_2 \rightarrow ImCH_2CH(COOC_2H_5)_2 \rightarrow ImCH_2CH_2COOH$$

<div align="right">

Imidazolyl-
propionic acid

</div>

Barger and Ewins (16) reduced imidazolylacrylic acid to this compound with sodium and alcohol.

Two patents describe the synthesis of imidazolylpropionic acid from glutamic acid by the Akabori method (11a, 93). Glutamic acid ester is reduced to the aminoaldehyde, which is condensed with thiocyanic acid and the product is then oxidized with ferric chloride in the usual fashion.

G. Urocanic acid

Urocanic acid, imidazolylacrylic acid, was discovered in 1874 by Jaffe (63) in the urine of dogs and coyotes. It is also formed in pancreatic protein digests (2, 60).

The first synthesis started from the alkaline treatment of ergothioneine (*q. v.*). The imidazole sulfur of the resultant acrylic acid (16) was oxidized away with nitric acid. Urocanic acid was also obtained in small yield by the action of trimethylamine on $ImCH_2CHClCOOH$. Akabori and coworkers (12) developed the following method:

$$ImCHO \xrightarrow[\text{pyridine}]{CH_2(COOH)_2} ImCH=CHCOOH$$

<div align="center">

Urocanic acid

</div>
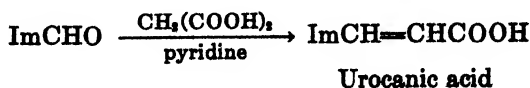
IV. OTHER IMIDAZOLES

A. Histamine analogs

This subject has been well reviewed by Guggenheim (45b) in his chapter on "Imidazolverbindungen."

Analogs of histamine are of interest principally because of their pharmacological possibilities. The difference in pharmacological activity between an amino acid and the amine resulting from decarboxylation is especially emphasized in the case of histidine and histamine. One would expect that derivatives of the carboxyl group of histidine might resemble histamine in their action. This expectation has been tested by Arai (13), who prepared histidine methyl ester and found a similarity to histamine in effects on blood pressure and smooth musculature. The action was, however, less marked.

In the homologous series of imidazolyl alkylamines, $Im[(CH_2)_n.NH_2$ (where $n = 1$ to 4), the greatest activity is found when $n = 2$. The only homolog which shows appreciable relative activity is the propyl compound ($n = 3$).

Pyman (87c) prepared the methyl homolog from his own supply of 2-thiolimidazolyl-4(or 5)-methylamine by oxidation. It was not possible to desulfurize with nitric acid, because the resultant nitrous acid would react upon the primary amino group. Ferric chloride was accordingly employed instead. Pyman prepared the butyl analog, but not the propyl, and concluded that imidazolylethylamine was the only active compound in the group.

Akabori was, however, able to prepare the propyl, as well as the butyl, analog by his aminoaldehyde method (page 55), and found the former to be fairly active (10, 11b). The starting materials for these syntheses were arginine and lysine. This is of incidental interest as an *in vitro* example of the suggested physiological convertibility of arginine to imidazole bodies, especially purines (7).

The two monomethyl derivatives of histamine (87c) are almost inactive. The same statement applies to 2-thiolhistamine. The latter compound is also an analog of thiolhistidine. Its synthesis (87g, 107) illustrates an utilization of the Bamberger reaction:
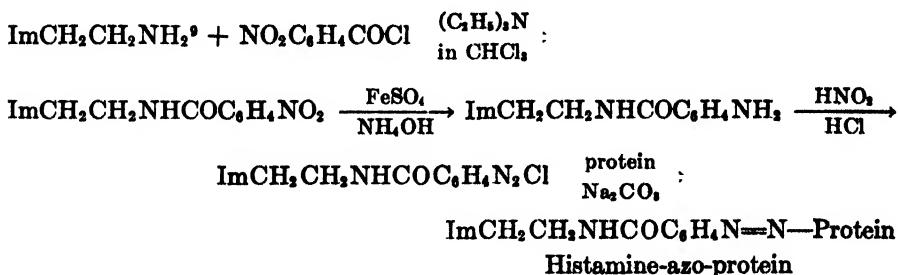

Thiolhistamine
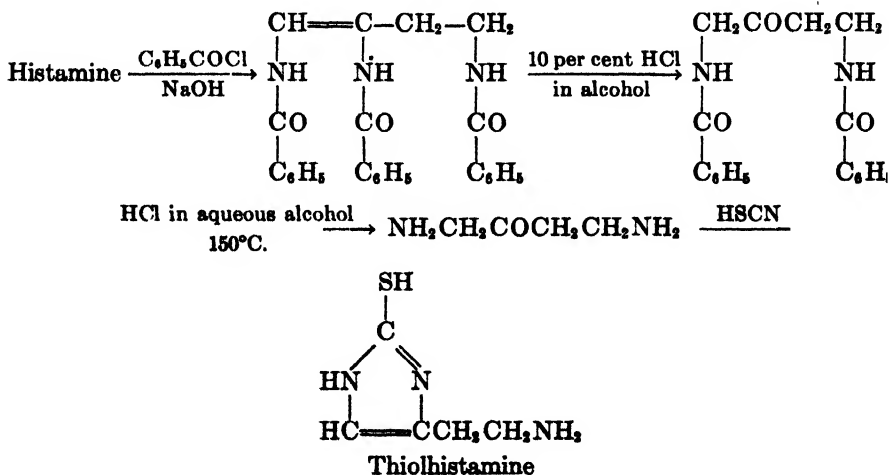
The histamine-like activity of the three isomeric β-pyridylethylamines has been studied (78, 102). Of these only the β-(2-pyridyl)ethylamine exhibited an

effect. The molecular fragment —CH═N—C(CH₂CH₂NH₂)═CH—, common to both this amine and histamine, has accordingly been postulated as the essential structure for the pharmacological activity.

B. Histamine-azo-protein

Since the release of histamine in the tissues is believed to be responsible for allergic manifestations (37b), attempts have been made to provide counteracting treatments as relief for asthma, hay-fever, etc. Desensitization by graded doses of injected histamine and the employment of histaminase have not (21b) provided a complete answer to this problem.
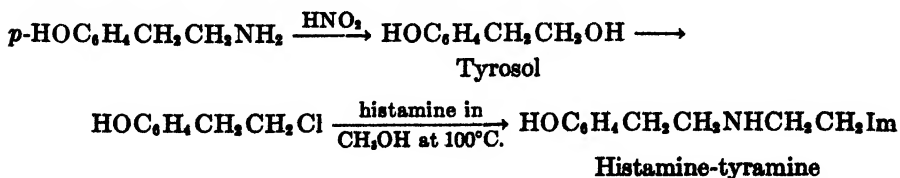
More encouraging results have been obtained by the provision of an immunity to histamine by the administration of histamine, as a hapten, coupled to protein (92). The rationale of this attack is based on the fact that proteins participate in almost all studied cases of antigenicity, and upon the pioneering work of Harington (52), who was able to elicit active antisera to thyroxine and aspirin by similar means. Of a number of coupling methods tried, the most practical seemed to be the following:

$$\text{ImCH}_2\text{CH}_2\text{NH}_2{}^{\bullet} + \text{NO}_2\text{C}_6\text{H}_4\text{COCl} \xrightarrow[\text{in CHCl}_3]{(\text{C}_2\text{H}_5)_3\text{N}} :$$

$$\text{ImCH}_2\text{CH}_2\text{NHCOC}_6\text{H}_4\text{NO}_2 \xrightarrow[\text{NH}_4\text{OH}]{\text{FeSO}_4} \text{ImCH}_2\text{CH}_2\text{NHCOC}_6\text{H}_4\text{NH}_2 \xrightarrow[\text{HCl}]{\text{HNO}_2}$$

$$\text{ImCH}_2\text{CH}_2\text{NHCOC}_6\text{H}_4\text{N}_2\text{Cl} \xrightarrow[\text{Na}_2\text{CO}_3]{\text{protein}} :$$

$$\text{ImCH}_2\text{CH}_2\text{NHCOC}_6\text{H}_4\text{N}═\text{N}—\text{Protein}$$
$$\text{Histamine-azo-protein}$$

The use of this compound is indeed a hopeful example in the fast-growing field of drug antisera production.

C. Histamine-tyramine

This interesting compound was prepared since it combines in one molecule two pharmacologically active compounds found together in ergot. No pharmacological data were reported, but the synthesis followed the plan below (33, 42b).

$$p\text{-HOC}_6\text{H}_4\text{CH}_2\text{CH}_2\text{NH}_2 \xrightarrow{\text{HNO}_2} \text{HOC}_6\text{H}_4\text{CH}_2\text{CH}_2\text{OH} \longrightarrow$$
$$\text{Tyrosol}$$

$$\text{HOC}_6\text{H}_4\text{CH}_2\text{CH}_2\text{Cl} \xrightarrow[\text{CH}_3\text{OH at 100°C.}]{\text{histamine in}} \text{HOC}_6\text{H}_4\text{CH}_2\text{CH}_2\text{NHCH}_2\text{CH}_2\text{Im}$$
$$\text{Histamine-tyramine}$$

D. Imidazolylacetic acid

This compound, ImCH₂COOH, has been suggested as a probable metabolic intermediate (44); thus it bears an analogy to indoleacetic acid, which is found
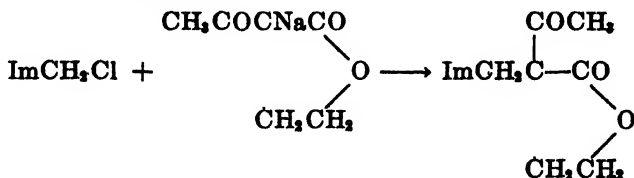

• Im = imidazolyl.

in urine and may arise entirely or in part from tryptophan. Imidazolylacetic acid was first synthesized by oxidation of imidazolyllactic acid (69) and later was obtained as a by-product in one of Pyman's histamine syntheses (87a).

E. Pilocarpine analogs

It is natural that several Russian workers have prepared analogs of pilocarpine. Information on the medical value of these compounds is unfortunately not available.

One analog uses acetobutyrolactone, a commercial thiamine intermediate, and (chloromethyl)imidazole (27):

$$ImCH_2Cl \; + \; \begin{matrix} CH_3COCNaCO \\ \diagdown \\ O \\ \diagup \\ CH_2CH_2 \end{matrix} \longrightarrow \begin{matrix} COCH_3 \\ | \\ ImCH_2C-CO \\ \diagdown \\ O \\ \diagup \\ CH_2CH_2 \end{matrix}$$

Some general syntheses of analogs have been patented (67). There is certainly considerable room for improving the medical situation regarding pilocarpine by cheapening its synthesis or by providing more readily available active analogs.
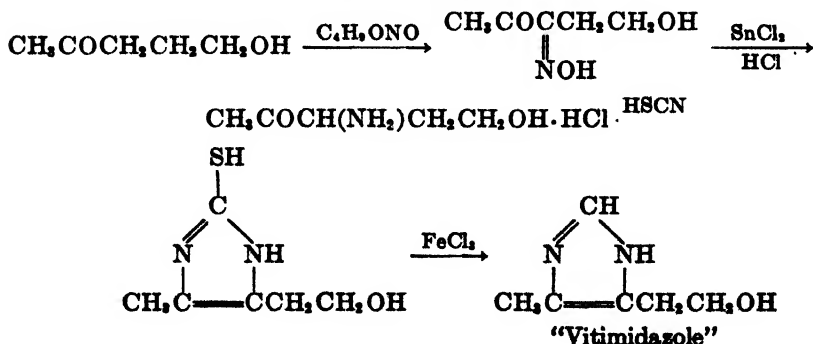
F. Sulfa imidazoles

No knowledge of useful sulfa compounds containing an imidazole nucleus has come to hand. Northey has reported negative tests (79) with sulfahistamine, and two British chemists with considerable experience in imidazoles have assigned a patent for the preparation of such derivatives (76). The process involves the conventional coupling of acylated sulfanilyl chloride and aminoimidazole, followed by deacylation.

G. "Vitimidazole"

The imidazole analog of thiamin thiazole has been synthesized in this laboratory (39). Before the structure of thiamin was elucidated, imidazolemethylethylcarbinol was actually claimed to be antineuritic (91). This was later disputed (48).

The synthetic process was carried out as follows:

$$CH_3COCH_2CH_2CH_2OH \xrightarrow{C_4H_9ONO} \underset{NOH}{\overset{CH_3COCCH_2CH_2OH}{\underset{\|}{}}} \xrightarrow[HCl]{SnCl_2}$$

$$CH_3COCH(NH_2)CH_2CH_2OH \cdot HCl \cdot \overset{HSCN}{}$$

$$\begin{matrix} SH \\ | \\ C \\ \diagup\diagdown \\ N \quad\;\; NH \\ \| \qquad | \\ CH_3C\!\!=\!\!=\!\!CCH_2CH_2OH \end{matrix} \xrightarrow{FeCl_3} \begin{matrix} CH \\ \diagup\diagdown \\ N \quad\;\; NH \\ \| \qquad | \\ CH_3C\!\!=\!\!=\!\!CCH_2CH_2OH \\ \text{"Vitimidazole"} \end{matrix}$$

When tested on *Phycomyces Blakesleeanus*, this compound lacked the characteristic activity of the analogous thiazole (22).

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THE NEED FOR REFORM IN INORGANIC CHEMICAL NOMENCLATURE[1]

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Lack of conformity of usage with formulated systems of inorganic nomenclature is discussed. Difficulties are encountered in indicating the proportions of constituents of compounds (either by valence or by stoichiometric composition), in varying usage of prefixes and suffixes, and in differences in the order of designating constituents. Nomenclature problems are pointed out relating to (*1*) elements, (*2*) groups such as alkaline earths and halides, (*3*) radicals or ions, and (*4*) certain classes of compounds. The classes considered are: intermetallic compounds, oxygen acids, salts (including acid and basic salts, double or multiple salts as con-

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trasted with complexes and molecular addition compounds, and salts with mixed halogen anions), molecular addition compounds (as hydrates and ammoniates), coördination compounds, and isopoly and heteropoly acids and their salts. Examples of miscellaneous compounds are also presented.

"Reform" is perhaps too strong a word, though even here, as in all questions of nomenclature, there is opportunity for disagreement. Delépine (21), in his report of the Commission for the Reform of the Nomenclature of Inorganic Chemistry in 1928, stated that "It has become legitimate to undertake, if not a reform, at least the suppression of all the vicious usages that have been introduced into the nomenclature." Not only should "vicious usages" be suppressed, but usages that in themselves can hardly be term "vicious," but that do conflict with a rational system of nomenclature, should be discouraged so far as possible. Can we agree that the ideal to be striven for is that the name for a given compound should definitely indicate the analytical composition and so far as possible the chemical structure? Yet some usages of long standing, though not ideal, have enough prestige on their side to counterbalance minor objections to them. It is such weighing of relative values that must be given careful consideration in any attempts at reform or change of a more or less drastic nature in the direction of systematization.

The oldest and most widely used names, and the names most difficult to change, are the common or trivial names. Such names always depend on memory, of course, and in some cases of complex compounds, with names based on the discoverer or on the color of the compound, for example, it is no mean feat to know off-hand the composition of a certain compound, such as Roussin's red salt, or to know which of the ammino cobalt chlorides is praseocobaltic chloride. Where common names refer to simpler specific compounds, involving no ambiguities or inconsistencies, there may be no objection to their use. Thus, if *lime* denotes only calcium oxide, well and good. However, a distinction must be made between common names used correctly and those that are used loosely or incorrectly or that are incorrect in themselves. Thus, the use of *lime* for calcium carbonate or any other compound of calcium is ambiguous and leads only to confusion. The term *alums* (14, 18) is applied to anhydrous double sulfates or to other hydrates than the 12 (or 24) H_2O, and also to aluminum sulfate itself. *Soda* and *potash* have been used for so many compounds that there can be no certainty with regard to them. *Saltpeter* may refer to any one of three nitrates.

Names like *phosphate of lime, bicarbonate of soda, alumina chloride*, and *potash prussiate*, formerly considered correct, are now ruled incorrect, though they are still all too common. *Carbonic acid* is still used for carbon dioxide, *sulfurous acid* for sulfur dioxide, and *phosphoric acid* for phosphorus pentoxide.

Mineral names are often used loosely for the synthetic compounds, even though these compounds may not have the crystal structure and other physical properties characteristic of the naturally occurring minerals. Synthetic sodium fluoaluminate, for example, is commonly called *cryolite*. *Borax* is not limited to the decahydrate of sodium tetraborate.

The increasing number of trade and trade-marked names only adds to the

confusion and to scattering in indexes. Different names may be introduced for the same substance, especially when it is intended for different purposes. Thus *Carbona* is carbon tetrachloride, but so is *Pyrene*.

However, the problems connected with common, mineral, and trade names are less intricate than 'those connected with strictly chemical or systematic names. It is the latter type that have occupied most of the attention of international committees for the reform of chemical nomenclature. New conceptions of structure, introduced particularly through physical-chemical, x-ray, and electron-diffraction studies, and new theories, especially the coördination theory, have indicated changes that should be made in long-established names. In the system approved for coördination compounds, the central atom is named last; this makes a few well-established names, notably *ferrocyanide* and *ferricyanide*, out of step. As early as 1923 the Nomenclature Committee of the British Chemical Society and that of the American Chemical Society agreed that *chloroplatinate* should be preferred to *platinichloride* and that, similarly, *chloroaurate* should be adopted. This rule should not be limited to these two classes of compounds, however. A well-known inorganic chemistry textbook, for example, has *chloroplatinic acid*, *chloroplatinate*, and *chloroplatinous acid*, but switches to *platinochloride* for K_2PtCl_4 and *platinocyanide* for $BaPt(CN)_4 \cdot 4H_2O$. *Fluosilicate* has replaced *silicofluoride* to a large extent, and *fluoborate* has replaced *borofluoride*, but *cobaltocyanide* and *cobalticyanide* (like *ferrocyanide* and *ferricyanide*) and *cobaltonitrite* and *cobaltinitrite* are still more common than the terms now considered correct. Heteropoly acids (and their salts) should also be named as coördination compounds: *molybdophosphoric acid* and *tungstophosphoric acid* should be used instead of *phosphomolybdic acid* and *phosphotungstic acid*. With some of the more complex heteropoly acids containing at least three significant elements the structure, or even the composition, often is not known and no suitable name can be selected.

Inconsistencies probably show up more readily in indexes than anywhere else. The great variety of compounds, from many sources over a period of years, in compilations like the *Decennial Indexes* of *Chemical Abstracts* is likely to lead to a great variety and inconsistency in names; consequently there is great need of guarding against scatterings. The possibilities of a variety of names for even a relatively simple compound may be surprisingly great. The word order in English names for salts, with the cations always first, is in some respects unfortunate, because the cations (particularly if simple) are likely to be of less interest than the anions, which exhibit greater variety in composition and wider discrepancies in names. Hence it has been found necessary in the *Chemical Abstracts* office to keep a file of names for anions in order to harmonize the names for cesium salts, for example, with those for sodium salts.

While it is agreed in English that the electropositive part of the name should come first, there is not complete agreement as to which is the more electropositive of two non-metallic elements. In only four of the reports of international committees (12, 13, 21, 48) has an electrochemical series for the non-metallic elements been given. These series do not agree in the positions of nitrogen and

sulfur and of oxygen and fluorine. With still other pairs of elements, as carbon and silicon, usage is not yet uniform. The last two international reports (53, 70) do not include any electrochemical series.

Some attempts at systematization of chemical names, notably Werner's logical system for coördination compounds, have not met with general favor because of difficulties in carrying them out. Only the Germans seem to be able to distinguish clearly in speaking among the four vowels selected by Werner to denote valence. Clumsy names like those used by Mellor can hardly make any great appeal even to the most technically trained.

Once the various nomenclature problems have been settled for a given compound and a suitable systematic name has been selected, there still remains the question of the written form (cf. Crane (29)). Often there is a choice in regard to the use of one or two or more separate words and the use of hyphens. *Sodium fluoaluminate* might be written as two or three words or the *fluo-* might be hyphenated. Increasing complexity in compounds naturally increases the possibilities of variation in the written form as well as in the name. American and British spellings of chemical words differ, notably in the use of *f* or *ph* and *aluminum* or *aluminium*. It is hoped that the publications of the American Chemical Society are the best standard for American practice.

Another problem closely related to that of nomenclature is the method of writing formulas. The order of symbols in formulas naturally follows the order of the words in the name. Thus in English the electropositive element or radical comes first, as $NaCl$, while in French the electronegative portion comes first, as $ClNa$. Furthermore, the order of symbols might well indicate the structure as far as possible; e.g., for cyanates and thiocyanates, —OCN and —SCN are preferable to —CNO and —CNS. Instead of subscripts to denote the number of atoms or groups present, the French often use superscripts. In some cases there is little uniformity in the matter of molecular weights represented by formulas. Formulas for alums are written with 12 or 24 H_2O, and for the simple molecules (as $KAl(SO_4)_2 \cdot 12H_2O$) or for addition compounds (as $K_2SO_4 \cdot Al_2(SO_4)_3 \cdot 24H_2O$). This question, like others, can be settled only by studies of structure. While formulas should logically conform to the names chosen and structures assumed, they do not always do so. Isopoly and heteropoly acids and salts may have (*1*) formulas representing only the analytical composition, (*2*) formulas resolved into the base anhydride and acid anhydride (70), or (*3*) formulas representing the structure at least in part. Trisodium dodecamolybdophosphate may accordingly be written as $Na_3PMo_{12}O_{40}$, $3Na_2O \cdot P_2O_5 \cdot 24MoO_3$, or $Na_3PO_4 \cdot 12MoO_3$. The use of brackets in coördination compounds has never been standardized, especially from the point of view of what to include within the brackets. Uncertainty is particularly marked with regard to molecules of water, as in ammino chromium complexes. The answers to many of these questions must be based again on the structure of the compounds. In all the cited types of inconsistencies in formulas, absolute standardization may not be advisable, since certain types of formulas may be selected in certain instances to bring out definite points under discussion. However,

where no such purpose is being served, greater standardization in formulas than now exists would seem desirable.

A final general matter related to nomenclature is that of variations and carelessness in pronunciation. If either à-mē′ nō or ăm′ I-nō is used for both NH_2 and combined NH_3 without discrimination, how is one to know which is meant? A report of the Nomenclature, Spelling and Pronunciation Committee of the American Chemical Society on "The Pronunciation of Chemical Words" was published in the *News Edition* in 1934 (39).

Of great primary importance in naming inorganic compounds is the indication of the proportions of constituents, by means of either the valence or the stoichiometric composition. Difference in valence has been most commonly in-

TABLE 1
Nomenclature of iron compounds

| OXIDES | HYDRATED OXIDES | | SALTS | |
	Formula	Name	Formula	Name
FeO	$FeO \cdot H_2O$ $Fe(OH)_2$	Ferrous hydroxide	M_2FeO_2	{ Hypoferrite Ferroate
Fe_3O_4				
Fe_2O_3	$Fe_2O_3 \cdot xH_2O$ $HFeO_2$ } $FeO(OH)$ } $Fe(OH)_3$	Hydrated ferric oxide Ferrous acid Ferric hydroxide	$MFeO_2$ } $M_2O \cdot Fe_2O_3$ }	{ Ferrite Metaferrite Ferrate Ferriate
(FeO_2)	(H_2FeO_3)		M_2FeO_3	{ Perferrite Ferrate
(FeO_3)	(H_2FeO_4)	Ferric acid	M_2FeO_4	{ Ferrate Perferrate Ferronate
(FeO_4)	(H_2FeO_5)		M_2FeO_5	Perferrate

dicated by the use of the suffixes *-ous* and *-ic* for cations and acids, and *-ite* and *-ate* for anions. When only two valences are involved, as with copper, this system is reasonably satisfactory, though it is necessary to remember the valences of the given element. With the iron compounds, the greatest confusion occurs in the anion names (see table 1). The prefixes *hypo-* and *per-* have been used in combination with the suffixes *-ite* and *-ate* to represent four or even five valency stages in the case of anions. Terms like *ferrosoferric, ferrosic,* and *ferriferrous* have been introduced for cations with more than two valences, or prefixes like *sub-* and *proto-* have been used, especially with names of oxides. With elements having as many different valences as manganese and rhenium, however, these makeshift systems break down (see tables 2 and 3). The names of

the manganites are in a confused state. The rhenium compounds that have caused the most trouble are those analogous in formula to the chloroplatinates and accordingly commonly called *chlororhenates*. Rhenium and platinum are not, however, chemically related, and the oxygen acid corresponding to M_2ReCl_6 is rhenous acid, H_2ReO_3.

Werner's system, based on the use of *a, o, i, e, an, on, in, en* for valences of one to eight, respectively, could be satisfactorily worked out only in German and never was generally adopted.

TABLE 2

Nomenclature of manganese compounds

OXIDES	SALTS		COMPLEXES	
	Formula	Name	Formula	Name
(Mn_2O)			$M_6Mn(CN)_6$	Double salt
MnO			$MMnCl_3$	Trichloromanganite
			M_2MnCl_4	Tetrachloromanganite / Double salt
			M_4MnCl_6	Double salt
Mn_3O_4				
Mn_2O_3	$MMnO_2$	Hypomanganite / Manganite	$MMnF_4$	
			M_2MnCl_5	Chlorohypomanganite / Double salt
			$M_3Mn(CN)_6$	Double salt
MnO_2	M_2MnO_3 $M_2Mn_2O_5$ $M_2Mn_3O_7$ $M_2Mn_4O_9$ $M_2Mn_5O_{11}$ etc.	Manganite / Permanganite	M_2MnCl_6	Chloromanganite / Manganichloride
MnO_3	M_2MnO_4	Manganate		
Mn_2O_7	$MMnO_4$	Permanganate		

A third system, the Stock system (1, 2, 3, 4, 5, 48, 53, 70), is based on the use of Roman numerals in parentheses following the cation or anion name. The ending *-ate* is then used wherever *-ite* or *-ate* was used before. Fe_3O_4 is accordingly called *iron(II, III) oxide* and K_2ReCl_6 is called *potassium chlororhenate(IV)*. This system is adopted in the 1940 Rules (70) but it has not yet been put into general use. The Roman numeral can be used with symbols as well as names by placing it above and to the right, as Cu^I salts.

Stoichiometric composition is almost invariably indicated by Greek prefixes through twelve, though there have been proposals to use Arabic numerals either

before or after the words making up the name (antimony-2 sulfide-3 or 2-antimony 3-sulfide) (13, 21). Even in the use of the Greek prefixes, however, there have been inconsistencies. *Di-* and *bi-* have both been used for two, and *octa-* and *octo-* for eight. The Latin prefixes *nona-* and *undeca-* have frequently replaced the Greek *ennea-* and *hendeca-*, respectively. *Hemi-* is used by some for half, but Mellor's *trita-*, *pentita-*, etc., for one-third, one-fifth, etc., respectively, are not in general use. *Sesqui-* is common for three-halves, especially

TABLE 3

Nomenclature of rhenium compounds

OXIDES	SALTS		COMPLEXES	
	Formula	Name	Formula	Name
Re_2O				
ReO				
Re_2O_4				
Re_2O_3	$MReO_2$	Hyporhenite	$MReCl_4$ M_2ReCl_5 M_3ReCl_6	Double salt Chlororhenite { Hexachlororheniate Double salt
ReO_2	M_2ReO_3	Rhenite	M_2ReCl_6	{ Chlororhenite Chlororhenate (Hexa)chlororheneate Rhenochloride Rhenichloride Double salt
(Re_2O_5)	M_3ReO_4 $MReO_3$ $M_4Re_2O_7$	Orthohyporhenate (Meta)hyporhenate { Pyrorhenate Pyrohyporhenate		
ReO_3	M_2ReO_4	Rhenate		
Re_2O_7	$MReO_4$ M_3ReO_5	(Meta)perrhenate Mesoperrhenate		

for oxides, but P_4S_3 has been called *phosphorus sesquisulfide*. If no numerical prefix is used before a prefix denoting substitution, *mono-* may be understood, as in *thiosulfate*, or complete substitution may be indicated, as in *thiocarbonate* (used sometimes for *trithiocarbonate*) and *chloroplatinate* (for *hexachloroplatinate*). Further, a numerical prefix sometimes indicates the total number of atoms of a given element or radicals in a compound and at other times the number of equivalents or the number of atoms relative to the number of atoms of another element. *Tricalcium phosphate* is $Ca_3(PO_4)_2$, but *dicalcium phosphate* is $CaHPO_4$.

Sulfur monochloride is S_2Cl_2. The number of atoms of the second element (as the sulfur) may be indicated or not. SO_3 and As_2O_3 are both called simply *trioxide*. With such simple familiar compounds as these, the inconsistencies are of minor importance, but similar instances among complex compounds like the iso- and hetero-poly acids may lead to confusion. Though less definite than the numerical prefixes, the prefixes *ortho-*, *pyro-*, *meta-*, etc., also serve to indicate the proportions of constituents. Their use will be considered later in connection with oxygen acids. Numerical prefixes may also indicate degree of polymerization, as in *sodium hexametaphosphate* $(NaPO_3)_6$.

Prefixes indicating the presence of specific radicals are used in three different ways in inorganic names. In the first place, they denote substitution, usually for oxygen or hydroxyl instead of for hydrogen as in organic names. Chloroplatinic acid, H_2PtCl_6, can be regarded as platinic acid, H_2PtO_3, in which six chlorine atoms have replaced the three oxygen atoms, or as the so-called hydroxy-(or hexahydroxy)platinic acid, $H_2Pt(OH)_6$, in which six chlorine atoms have replaced the six hydroxyl groups. The intermediate, partially substituted acids are also known and named as *chlorohydroxy*(or *chlorohydroxo*)*platinic acids*, e.g., $H_2Pt(OH)_5Cl$, *chloropentahydroxyplatinic acid*. The ambiguous use in these cases of *chloro-* without a numerical prefix, to indicate either complete substitution (H_2PtCl_6) or substitution of only one group ($H_2Pt(OH)_5Cl$) leads to the redundant use of the prefix *hydroxy-* or *hydroxo-*. The presence or number of hydroxyl groups or oxygen atoms is not ordinarily indicated in the names of oxygen acids (*hydroxyplatinic acid* is an exception). HPO_3 is not called *hydroxydioxyphosphoric acid*, though the prefix *meta-* is used to indicate that this is the least hydroxylated of the common acids of phosphorus. The monofluoro derivative, H_2PO_3F, however, has been called both *fluodihydroxyphosphoric acid* and *monofluorophosphoric acid*. For the difluoro derivative, HPO_2F_2, even though *difluo-* or *difluoro-phosphoric acid* is unambiguous, *difluodioxyphosphoric acid* has seemed better to some writers. Sometimes the prefix *meta-* is used with these phosphoric acid derivatives, but more often it is not. $CsPF_6$, for instance, has been called *cesium fluometaphosphate*, *cesium hexafluometaphosphate*, and *cesium hexafluophosphate*. A curious example of what might be termed backward substitution occurs with a difluoro derivative of boric acid. If fluoboric acid, HBF_4, is considered a completely substituted metaboric acid, then the difluoro derivative, $H_3BO_2F_2$, would be a partially substituted orthoboric acid and could be named *difluoboric acid*. The common name, however, seems to be *dihydroxyfluoboric acid*, based on the replacement by hydroxyl of two fluorine atoms in fluoboric acid, HBF_4. Also of interest at this point is the variation in the use of *hydro-* with names of complex acids. Thus *fluosilicic acid* and *hydrofluosilicic acid* are synonymous, as well as *ferricyanic acid* and *hydroferricyanic acid*.

Prefixes are also used in inorganic chemistry to indicate replacement of hydrogen (as in *dihydroxyammonia*, $NH(OH)_2$) and of other atoms and groups. In certain cases, discussed later, of compounds of boron, germanium, and silicon the prefixes *boro-*, *germano-*, and *silico-* denote replacement of carbon by these

elements. The prefixes *alumino-*, *boro-*, *beryllo-*, etc., are supposed to be used for complex silicates only when these elements replace silicon (70).

Besides denoting substitution, prefixes are used in the second place to denote simply the presence of an atom or radical, not necessarily attached to the constituent denoted by the word to which the prefix is attached. Names like *phosphorus dichlorotrifluoride* for PCl_2F_3 are allowable according to the 1940 Rules (70), though the chlorine and fluorine atoms are all bound to phosphorus and the compound is as much a chloride as a fluoride. Here the prefix seems to mean "chloride and."

The third use of prefixes is to denote addition in a complex. $CsICl_2$, in which the chlorine atoms are attached to the iodine and not to the cesium, is called *cesium dichloroiodide*, but might also be given the name *cesium dichloro*(or *chloro*)*hypoiodite*, a name denoting substitution.

There is also disagreement as to what prefixes should be used to denote the presence of a given group. Correct decisions must often depend upon determinations of structure. *Nitro-* and *nitrito-*, designating the groups NO_2^- and ONO^-, respectively, have both been used in naming complexes like $K_3Co(NO_2)_6$ (commonly called *potassium cobaltinitrite*). *Per-* is used for acids and salts derived from hydrogen peroxide and also for those derived from the highest oxidation stages of some elements. *Persulfuric acid*, because it contains the —O—O— linkage, is an example of the former type, for which the rules of the international committee recommend the use of the prefix *peroxy-*, and *perchloric acid* is an example of the latter type. *Thio-* and *sulfo-* have both been used to denote replacement of oxygen by sulfur, but *sulfo-* in organic chemistry refers to the —SO_3H radical.

More minor differences in prefixes also exist. *Hydroxy-* and *hydroxo-* are both used for —OH, *hydroxo-* usually in complexes. A similar situation exists for *oxy-* and *oxo-*. *Halo-* and *halogeno-* have been used interchangeably; so have *fluo-*, *fluor-* and *fluoro-*. The connecting vowels *o* and *a* are sometimes kept and sometimes dropped. *Chloroaurate* and *chloraurate* are both found, and so are both *metaantimonite* and *metantimonite*.

Suffixes, like prefixes, are used sometimes to denote substitution and sometimes to denote combination of atoms or groups. In *aminetrisulfonic acid*, $N(SO_3H)_3$ (also called *nitrilo(tri)sulfonic acid*), the *-sulfonic* denotes substitution of —SO_3H for hydrogen in ammonia (since *amine* is regarded as equivalent to *ammonia*). Names of the type of *aminetrisulfonic* are approved in organic chemistry (e.g., *benzenesulfonic acid* instead of *phenylsulfonic acid*), but are rare in inorganic chemistry. On the other hand, the name *chlorosulfonic acid* for $ClSO_3H$ simply indicates that chlorine and —SO_3H have combined. (*Chlorosulfuric acid*, analogous to *chlorophosphoric*, *chloroplatinic*, etc., has also been used for $ClSO_3H$.)

Minor differences in suffixes seem to consist chiefly of the use or omission of *i* before *-ous* and *-ate*. *Antimonious* and *antimonous*, *antimoniate* and *antimonate* all occur. *Selenious* and *tellurous* are the common terms in each case, but are inconsistent with each other. In names of coördination compounds

containing trivalent central atoms the *i* of the Werner system is common, as in *cobaltiate*. The *i* is sometimes used even in a name having Roman numerals to indicate valence according to the Stock system. The English and German versions of the 1940 Rules have *potassium hexanitrocobaltiate(III)*, but this *i* was taken out in the American version because it seemed superfluous.

The order of naming constituents may also vary. Reference was made earlier to binary compounds of non-metallic elements. The hydrides are an outstanding example of variation. *Hydrogen sulfide* is, of course, common for H_2S (or still sometimes the older *sulfuret(t)ed hydrogen*), while *boron hydrides* (or sometimes *hydroborons*) is used for the compounds of boron and hydrogen. P_2H_4 has been called both *phosphorus dihydride* and *hydrogen phosphide*. A general question of alphabetical order *vs.* an order based on some chemical property, as electropositivity, comes up with names for double salts, coördination compounds as ammino compounds, heteropoly acids, and complex mixed halides. Again, the ammonobasic compound $HgNH_2Cl$, infusible white precipitate, can be called *mercury amidochloride* (analogous to *mercury hydroxychloride*), *amidomercury chloride*, or *mercury amide chloride*. In dealing with the complex mercury ions, on the other hand, it seems more natural to say *amido-* and *hydroxymercuric* or *-mercury*.

A more detailed examination of inorganic chemical nomenclature naturally begins with the names and symbols for the individual elements. Inconsistencies in this domain have been dealt with by the International Committee on Atomic Weights rather than the Committee on Inorganic Chemical Nomenclature, but it might be well to note a few of the cases here. Outstanding are *beryllium* and *glucinum*, and *columbium* and *niobium*. Among variations in symbols are *Ac* and *Act* for *actinium*, *Az* (still used to some extent in French) and *N*, *Tu* and *W*, *J* (in German) and *I*, *Ar* and *A*, *X* and *Xe*, *Em* and *Rn*, *Tu* and *Tm*, and *Cy* (in German) and *CN* for the cyano radical. This variation in symbols prevents formula indexes from ideally overcoming language as well as nomenclature indexing difficulties. Numerals used with atomic symbols to indicate mass, atomic number, and state of ionization have not always had the same positions around the symbol.

In recent years the discovery of isotopes has introduced another problem into the naming of both elements and compounds (42, 45). The hydrogen isotopes are, of course, the outstanding example. The confusion of names that arose almost at once for "heavy hydrogen," its nucleus, and its compounds (32, 33, 40, 41, 43, 44) was in large part dispelled by prompt action of the American Chemical Society Committee (47) in favor of *deuterium*, *deuteron*, and modified Boughton names (e.g., *ammonia-d* for NH_2D), respectively.

Names of groups of elements or compounds vary to some extent. The alkali metals are loosely called *alkalies*, and the alkaline-earth metals *alkaline earths*. In names of compounds, however, there is no objection to phrases like *alkali chlorides* or *alkaline-earth sulfates*. There have been suggestions to prefer *hydrogenides* to *hydrides* and *halogenides* to *haloids* or *halides* (the 1940 Rules recommend *halogenides*). Peroxides have been called *superoxides* and *hyper-*

oxides, and higher oxides like lead dioxide and manganese dioxide, which do not contain the —O—O— linkage, have been wrongly termed *peroxides*. Acid-forming oxides are appropriately called *anhydrides* (*sulfuric anhydride* for sulfur trioxide) or, as noted earlier, not so appropriately given the names of the corresponding acids. Hydrated oxides may be named as such or as *hydroxides* or *acids*. With amphoteric elements like aluminum and iron, all three types of names have been applied to the same compounds. Metal hydroxides are still incorrectly called *hydrates* at times, as *barium hydrate* instead of *barium hydroxide* for $Ba(OH)_2$. Certain oxides, like Fe_3O_4 and Pb_3O_4, can be regarded as salts and so named (*ferrous ferrite*, $Fe(FeO_2)_2$, and *plumbous plumbate*, Pb_2PbO_4). Salts of nitrogen compounds, as hydrazine, have been variously named. Acid sulfides are known as both *hydrosulfides* and *sulfhydrates*. Thiocyanates are still called *sulfocyanates* and *sulfo-* or *thio-cyanides*. *Sulfoxide*, which has a definite use in organic chemistry for compounds containing the $\rangle SO$ group, has been applied to the oxysulfide $P_4S_4O_6$. Acetylides like Cu_2C_2 and HgC_2 are frequently designated by the more general term *carbide*, and azides like $Pb(N_3)_2$ by *nitride*. *Hyponitrite* and *nitrosyl* both refer to compounds like $Ag_2(NO)_2$ containing the —NO group.

In connection with group names it is of interest to note the illogical use of *monoacid, diacid*, etc., in reference to bases, and of *monobasic, dibasic*, etc., in reference to acids. *Monohydric, dihydric*, etc., have been used for bases, acids, alcohols, and phenols. Some writers are now using *monoacid, diacid*, etc., to replace *monobasic acid, dibasic acid*, etc., and *monobase, dibase*, etc., to replace *monoacid base, diacid base*, etc.

Names for inorganic radicals and ions vary unnecessarily, and in some cases there is confusion between organic and inorganic usage (see table 4). *Amido-* and *amino-* are supposed to be distinguished in organic chemistry, but do not seem to be in inorganic chemistry; a similar situation exists with *imido-* and *imino-*. There has been much disagreement over the naming of $[H_3O]^+$, for which the 1940 Rules favor *hydronium*. Even the question of *when* to use a radical name at all has not been settled for inorganic compounds, particularly the basic salts. Thus $POCl_3$ is called *phosphorus oxychloride* slightly more frequently than it is *phosphoryl chloride*. Yet for the corresponding sulfur compound, *thiophosphoryl chloride* seems the most satisfactory name. Some elements with several valences, notably molybdenum and vanadium, form radicals with varying valence, which have usually not been distinguished by specific names.

Certain classes of compounds, as indicated in the various committee reports, have given rise to special difficulties in nomenclature. Intermetallic compounds, because of the variability and indefiniteness of their composition, are particularly troublesome. Suggestions have been made to name them in alphabetic order or in any order, with Arabic numerals to indicate the stoichiometric composition, if known. The 1940 Rules recommend the avoidance of names and the use of only formulas, as definite as possible. For compounds of indefinite or varying composition (non-Daltonian compounds) a bar placed above the formula is

TABLE 4
Nomenclature of inorganic radicals

RADICAL	NAME	RADICAL	NAME
NH₂—	Amido- Amino-	HO—	Hydroxy- Hydroxyl Hydroxo-
NH₄—	Ammonium	NH—	Imido- Imino-
SbO—	Antimonyl Antimony oxy-	OCN—	Isocyanato-
AsO—	Arsenyl	CN—	Isocyano-
BiO—	Bismuthyl Bismuth oxy-	SCN—	Isothiocyanato- Isothiocyano- Isosulfocyano-
BO—	Boryl	I—	Iodo-
Br—	Bromo-	IO—	Iodoso-
CO—	Carbonyl Carbon oxy-	IO₂—	Iodoxy-
Cl—	Chloro-	MoO— MoO≡ MoO≡	Molybdenyl Molybdenum oxy-
ClO—	Chloryl		
CbO≡	Columbyl Columbium oxy-	MoO₂—	Molybdenyl Molybdenum dioxy-
CrO₂—	Chromyl Chromium dioxy-	MoO(OH)—	Molybdyl
NCO—	Cyanato-	NO₃—	Nitrato-
NC—	Cyano-	N≡	Nitrilo-
F—	Fluoro- Fluo-	ONO—	Nitrito- Oxynitroso-
GeO—	Germanyl Germanium oxy-	N(OH)₃— ..	Nitronium
N₂H₄—	Hydrazinium	NO—	Nitrosyl Nitroso- Nitrogen oxy- Oximido-
N₂H₅—	Hydrazonium Hydrazinium	NO—	Nitrosyl
N₂H₆—	Hydrazonium Hydrazinium	NO—	Nitrosyl Nitroso-
H₂O—	Hydronium Hydroxonium Oxonium	N(OH)— ...	Nitrosyl Isonitroso- Hydroxynitrilo- Nitrilohydroxy- Oximido-

TABLE 4—*Continued*

RADICAL	NAME	RADICAL	NAME
NO_2—	Nitryl Nitroxyl Nitro-	SnH_3—	Stannyl
O—	Oxy- Oxo-	SnO—	Stannyl Tin oxy-
MnO_3—	Permanganyl	H_2NO_2S—	Sulfamyl
NP=	Phosphonitrile Phosphonitrilic	SO_4—	Sulfato-
PH_4—	Phosphonium	SH—	Sulfhydryl Hydrosulfuryl
PO—	Phosphoryl	SH_3—	Sulfonium
PO≡	Phosphoryl Phosphorus oxy-	SO_2—	Sulfuryl Sulfur oxy-
PO_2—	Metaphosphoryl	S_2O_5—	Pyrosulfuryl
P_2O_5≡	Pyrophosphoryl Diphosphorus trioxy-	Te—	Telluro-
Se—	Seleno-	TeO—	Telluryl Tellurium oxy-
$NCSe$—	Selenocyanato- Selenocyano-	S—	Thio- Sulfo- Thiol- (replacing O in OH) Thiono- Thione- } (replacing O in CO)
SeH—	Selenyl	SC—	Thiocarbonyl
SeO—	Selenyl Selenium oxy-	SC≡	Thiocarbonyl
SeO_2—	Selenyl Selenonyl Selenium oxy-	NCS—	Thiocyanato- Thiocyano- Sulfocyano-
SiH_3—	Silicyl Silyl	NOS—	.Thionitro-
SiO—	Silicyl Siliconyl Silicocarbonyl	NS—	Thionitroso- Thiasyl
Si_2O_3—	Disilicyl	SO—	Thionyl Sulfurous oxy-
SiH_2=	Silicylene	SP≡	Thiophosphoryl Phosphorus thio- Phosphorus sulfo-
NaO	Sodyl		

<div align="center">TABLE 4—Concluded</div>

RADICAL	NAME	RADICAL	NAME
$P_2S_3\equiv$	Thiopyrophosphoryl	VO—	Vanadyl Vanadium oxy-
ThO—	Thoryl Thorium oxy-	VO≡	Vanadyl Vanadylic Vanadium oxy-
TiO—	Titanyl Titanium oxy-	V_2O_3— $V_2O_3\equiv$ ...	Divanadyl Vanadium dioxy-
WO≡	Tungstyl Tungsten oxy-	ZrO—	Zirconyl Zirconium oxy-
UO_2—......	Uranyl		
VO—	Vanadyl Vanadylous Vanadium oxy-		

intended to prevent confusion with compounds of definite composition (Daltonian compounds).

Oxygen acids are often called *oxy acids*, a term which is also used for *hydroxy acids* in organic chemistry. Again, the extent of hydration has not been consistently indicated by the use of the prefixes *ortho-*, *pyro-*, *para-*, *meso-*, and *meta-*. The *ortho acid* should be the form of highest possible hydration, but is often the highest hydrated known form or the highest hydrated of the common forms (e.g., H_3PO_4 instead of H_5PO_5). The *pyro acid* should be intermediate between the ortho and meta acids, but *pyroboric acid* ($H_2B_4O_7$) contains less water than metaboric acid (HBO_2) and is therefore better called *tetraboric acid*. The acid $H_6B_4O_9$ can be properly called *pyroboric acid*, but this only adds to the confusion. Reference has already been made to difficulties in the use of the suffixes *-ic* and *-ous* and the prefixes *hypo-*, *per-*, *peroxy-*, *thio-*, and *sulfo-*.

The oxygen acids taken up in the committee reports are the sulfur, nitrogen, phosphorus, and boron acids. The most notorious case is that of $H_2S_2O_4$ (table 5), originally named *hydrosulfurous* because its salts were mistakenly thought to contain hydrogen. Later, it was called *hyposulfurous acid*, a name which has also been applied to $H_2S_2O_3$ (better called *thiosulfuric acid*). A still later name, *dithionous acid*, is adopted in the 1940 Rules, but it is objected to by some on the basis that the compound does not have a symmetrical structure, as does dithionic acid. Others maintain that it does have a symmetrical structure. Agreement on a suitable name for $H_2S_2O_4$ may have to await agreement on the structure.

Among the other oxygen acids and salts that have received more than one name are *pyrosulfurous*, $H_2S_2O_5$ (the salts are often called *metabisulfites* or sometimes *metasulfites*), *pyrosulfuric* or *disulfuric*, $H_2S_2O_7$ (there are other cases of inconsistent uses of *pyro-* and *di-*), and *nitroxylic* or *hydronitrous acid*, H_2NO_2.

Salt names regularly end in -*ate*, -*ite*, or -*ide*. As mentioned earlier, incorrect names based on the oxide instead of the metal (phosphate of *lime* instead of *calcium*) have not yet dropped out of use.

In naming acid salts, the variety of terms used leads to needless confusion. *Acid, hydrogen, hydro-, bi-,* and *bin-* may all mean that only one hydrogen atom in a diacid such as sulfuric acid has been replaced. With salts of triacids, e.g., the calcium phosphates, the variety of names is amazing and appalling. The use of the prefix *bi-* is particularly objectionable, because *bi-* is still used sometimes to indicate the presence of two atoms or radicals, as in *bichloride of mercury*.

<div align="center">

TABLE 5

$H_2S_2O_4$ *and its sodium salt*

</div>

(SOH)HO hydrosulfurous acid (Schützen-berger (1869, 1873))		S(NaO,HO)	(acid) hydrosulfite
		S(NaO)$_2$	neutral hydrosulfite
$H_2S_2O_4$ (Bernthsen (1881–1910), Bazlen, Nabl, Moissan, and others)		Na$_2$S$_2$O$_4$	
hyposulfurous acid (Roscoe (1877), Wagner (1877), and others)			hyposulfite
dithionous acid (A. A. Noyes and Steinour (1929); 1940 Rules)			dithionite
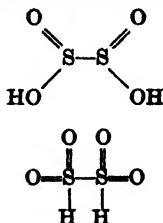
Symmetrical structures   *Unsymmetrical structures*
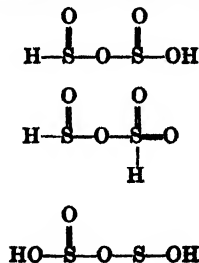
Basic salts can be named as such or as addition compounds of a salt with a hydroxide or oxide. Salts containing hydroxyl are named by prefixing *hydroxy-* (sometimes *hydroxo-*) to the anion name, and salts containing oxygen are named by prefixing *oxy-* (less often *oxo-*) (e.g., *bismuth oxychloride*) or by adding -*yl* to the cation name to form a radical name (e.g., *bismuthyl chloride*). The prefix *sub-* is attached to the names of some basic bismuth salts (e.g., *bismuth subnitrate*).

Double or multiple salts may be regarded as such, as complexes, or as molecular addition compounds. There is no sharp line that can be drawn at present. Shall it be *sodium aluminum fluoride*, $3NaF \cdot AlF_3$, *sodium fluoaluminate*, Na$_3$AlF$_6$, or *compound of aluminum fluoride with sodium fluoride?* Again, shall it be *sodium silver thiosulfate* or *sodium argentothiosulfate* (better, *thiosulfatoargentate*)?

The general tendency now seems to be to favor complexes, but there is as yet nothing approaching uniformity.

If it has been decided to name a compound as a double salt, there still remain a number of choices. The order of naming the cations or anions may be alphabetical; it may be based on the relative weight, valence, or interest of the elements or groups involved (the heavier, trivalent, and more significant element, as aluminum, chromium, or iron, is usually named first in alums); or it may follow the order of decreasing electropositivity (for cations) or increasing electronegativity (for anions), as recommended in the 1940 Rules. Names like *lead chlorofluoride*, as well as *lead chloride fluoride*, are permissible.

The similarity in names for the two types of mixed halogen anions, those in which the halogen atoms are attached to each other and those in which they are not, was discussed in connection with the use of prefixes in names like *cesium dichloroiodide* and *phosphorus dichlorotrifluoride*.

Molecular addition compounds, as hydrates and ammoniates, are not always readily distinguished from complexes. This failure leads to inconsistencies in naming and formulating these compounds. Compounds containing water in complexes are more properly considered *aquo complexes* than *hydrates*, and those with ammonia in complexes are *ammines* rather than *ammoniates*, though the term *ammines* has served to cover both types. Greek prefixes or Arabic numerals indicate the number of molecules of water or ammonia in the addition compounds. Compounds with hydrogen peroxide have been called *hydroperoxides*, *peroxyhydrates*, and *perhydrates*. Other types of addition compounds are designated as *compounds with aluminum chloride, nitrous oxide*, etc., or are represented simply by formulas.

Coördination compounds, especially the more complex ones, naturally offer opportunities for greater variation in systematic names than simpler compounds. Only a few general observations will be made here regarding compounds of this type. In the first place, the designations for the constituents of the compounds vary. The valence of the central atom has been indicated in anions by the insertion of only *o-* or *i-* or by the Werner system, or in either cations or anions by Roman numerals (Stock system). Of the neutral coördinating groups, ammonia has had applied to it or proposed for it the terms *ammine, ammino-, ammonio-, ammoniac, amman, ammono-*, and (in French) *-ammonique* at the end of complex cation names. Water is usually *aquo-*, but at the end of complex cation names it may be designated in French by *-aque* or *-hydrique*. *Pyridino-, pyridine*, and *-pyridique* (French) have all been used. Names for negative or acidic groups usually end in *o-* (*chloro-, nitro-, sulfato-*), but at the end of complex anion names salt endings (*chloride, nitrite, sulfate*) are sometimes used.

In the second place, the order in which the constituents are named varies. The same order of naming acid groups, neutral groups, and central atoms may be used for all types of complexes (as recommended in the 1940 Rules), or the order may vary depending on whether the compounds contain complex cations or complex anions or are non-electrolytes (as recommended in the Delépine reports of 1926 and 1928 (12, 21)).

In the third place, the components of the names of complexes may have special endings for complex cations and anions, or they may have none. Ordinarily, except in French, no endings are used for complex cations. Thus $[Cr(H_2O)_6]Cl_3$ is *hexaaquochromium(III) chloride*. For complex anions, however, the endings *-ite* and *-ate* are added to the central atom (*cobaltate, platinate*), or salt endings are used (*chloride, nitrite*). For complex acids, the endings *-ic* and *-hydric* are found and also, in German, no endings, whereas the 1940 Rules in English give, e.g., hydrogen hexachloroplatinate.

A further complication not even mentioned in the committee reports is introduced by stereoisomerism.

The isopoly and heteropoly acids and their salts present some of the same problems as the oxygen acids, chiefly with reference to the uses of the prefixes *ortho-* and *pyro-* and the numerical prefixes. The numerical prefix may indicate either the number of atoms of the significant elements or the number of molecules of anhydrides in the resolved formulas. For example, $Na_2B_4O_7$, incorrectly called *sodium pyroborate*, can be called *disodium tetraborate* (from the empirical formula) or *sodium diborate* (from the resolved formula, $Na_2O \cdot 2B_2O_3$). Another method of naming based on the resolved formulas makes use of Arabic numerals in parentheses to indicate the ratio of base anhydride to acid anhydride. By this system sodium tetraborate becomes *sodium (1:2) borate*).

These same problems are increased with heteropoly acids and salts by the presence of two or more significant elements. The question of order of naming constituents (*phosphomolybdate vs. molybdophosphate*) is added to the problem of indicating proportions of constituents. Because of their complexity and the lack of knowledge regarding their structure, heteropoly acids and their salts have proved about the toughest class of compounds to name systematically. Indeed, the international committees have never gone into this matter very thoroughly, though the latest reports give some discussion and examples.

Although a discussion of terms in connection with the newer concepts of acids, bases, and salts (50, 68) might be in place here, the decision of the German Nomenclature Commission (48) seems wise, namely, to limit its work to the problems of *nomenclature* and not to deal with definitions of terms, or to discuss "such questions as: how to define a base, or: in what way to differentiate between 'association' and 'polymerization'".

There still remain many miscellaneous groups of compounds and specific compounds that present interesting problems in nomenclature. A few of these seem worth brief consideration here. Compounds analogous to carbon compounds, with boron, germanium, silicon, etc., in place of part or all of the carbon, have been variously named, sometimes on the basis of this analogy (see table 6). The italicized names are used in *Chemical Abstracts* for the hydrides of germanium and silicon and for the derivatives of the boron and silicon hydrides. *Chemical Abstracts* practice is not meant to be the final word in nomenclature, but in indexing it is necessary to make a choice. The more rules that are generally agreed upon and are of reasonable ease of application, the simpler becomes the indexer's task. With metallic elements like germanium, lead, and tin, in accordance with a rule of the Commission on the Reform of the Nomenclature of

TABLE 6

Nomenclature of compounds analogous to carbon compounds

CARBON COMPOUNDS		BORON COMPOUNDS		GERMANIUM COMPOUNDS		SILICON COMPOUNDS	
Formula	Name	Formula	Name	Formula	Name	Formula	Name
CH_4	Methane	$(BH_3$ $(BH_4$	*Borine)* *Borane* Monoborane)	GeH_4	*Germane* Monogermane Germanomethane	SiH_4	*Silicane* Silane Silicomethane
C_2H_6	Ethane	B_2H_6	*Diborane* Boroethane	Ge_2H_6	*Digermane* Germanoethane	Si_2H_6	*Disilicoethane* Silicoethane Disilicane Disilane
C_3H_8	Propane	$(B_3H_{}$	Triborane)	Ge_3H_8	*Trigermane* Germanopropane	Si_3H_8	*Trisilicopropane* Silicopropane Trisilicane Trisilane
C_4H_{10}	Butane	B_4H_{10}	*Dihydrotetraborane* Tetraborane Borobutane			Si_4H_{10}	*Tetrasilicobutane* Silicobutane Tetrasilicane Tetrasilane
$CHCl_3$	Chloroform			$GeHCl_3$	*Trichlorogermane* Germanium chloroform	$SiHCl_3$	*Trichlorosilicane* Trichlorosilane Trichlorosilico- methane Silicochloroform
CH_3OH	Methanol					SiH_3OH	*Silicol* Silicanol

Organic	Boron	Germanium	Silicon
C_2H_5OH — Ethyl alcohol	B_2H_5OH — Diboranol		$(SiH_3)_2O$ — *Silicyl oxide* Disiloxane
$(CH_3)_2O$ — Methyl ether			
$HCHO$ — Formaldehyde			$(HSiHO)_x$ — *Silicoformaldehyde* Prosiloxane
$HCOOH$ — Formic acid		$HGeOOH$ — *Germanoformic acid*	$HSiOOH$ — *Silicoformic acid* Monosilanic acid
CH_3COOH — Acetic acid	$CH_3B(OH)_2$ — *Methaneboronic acid* Methylboric acid Dihydroxymethylborine	CH_3GeOOH — *Methanegermanonic acid* Germanoacetic acid	CH_3SiOOH — *Methanesiliconic acid* Methylsiliconic acid Methylsilicic acid Silicoacetic acid
C_2H_5COOH — Propionic acid	$C_2H_5B(OH)_2$ — *Ethaneboronic acid* Ethylboric acid	C_2H_5GeOOH — *Ethanegermanonic acid* Germanopropionic acid	C_2H_5SiOOH — *Ethanesiliconic acid* Ethylsilicic acid Silicopropionic acid Siliciproprionic acid
C_6H_5COOH — Benzoic acid	$C_6H_5B(OH)_2$ — *Benzeneboronic acid* Phenylboric acid Dihydroxyphenylborine Phenylboron dihydroxide	C_6H_5GeOOH — *Benzenegermanonic acid* Phenylgermanonic acid Germanibenzoic acid	C_6H_5SiOOH — *Benzenesiliconic acid* Silicobenzoic acid

TABLE 6—(*Concluded*)

CARBON COMPOUNDS		BORON COMPOUNDS		GERMANIUM COMPOUNDS		SILICON COMPOUNDS	
Formula	Name	Formula	Name	Formula	Name	Formula	Name
$Ca(CN)_2$......	Calcium cyanide					$Ca(SiN)_2$......	*Calcium silico-cyanide*
$CaCN_2$......	Calcium cyanamide					$CaSiN_2$......	*Calcium silico-cyanamide*

Organic Chemistry (31), names for organic derivatives are now based on the name of the element (e.g., *tetraethyllead*) instead of names of hydrides (*germane*, *plumbane*, *stannane*). Such compounds and also the compounds shown in the tables containing both carbon and boron, germanium, or silicon lie outside the province of this discussion.

The carbonyl and nitrosyl compounds, though belonging to the coördination compounds, are of special interest because the metal atom has an apparent valence of zero (see tables 7 and 8). Few names have even been proposed for these compounds.

Many other nitrogen compounds, because of their great variety, give rise to varied problems in naming. A general problem is how much to favor *ammono* names based on the analogy with the aquo system. The nitrogen compounds of phosphorus and sulfur will be discussed in a later paper.[3] Derivatives of

TABLE 7

Nomenclature of iron carbonyl compounds

FORMULA	NAME	FORMULA	NAME
$Fe(CO)_3$.............	Tricarbonyl	$Fe(CO)_4H_2$.............	Iron carbonyl hydride Hydrogen iron carbonyl
$Fe(CO)_3(NH_3)_2$			
		$Fe(CO)_4Hg.$	Mercury iron tetracarbonyl
$Fe(CO)_4$.............	Tetracarbonyl	$Fe(CO)_4Hg\cdot HgX_2$	
$[Fe(CO)_4]_3$..........	Dodecacarbonyl		
$Fe_2(CO)_9$	Enneacarbonyl Nonacarbonyl	$Fe(CO)_5\cdot HgCl_2$	
		$[Fe(CO)_3X_2]_3$	
		$Fe(CO)_4X_2$	
$Fe(CO)_5$.............	Pentacarbonyl	$Fe(CO)_5X_2$	Carbonyl halide
		$Fe_2(CO)_7X_4$	
$Fe(CO)_4NH_3$........			
		$M_2[Fe(CN)_5CO]$	

hydrazine and hydroxylamine have been named in many ways. The acid HN_3 has been called *hydrazoic acid*, *hydronitric acid*, and *azoimide*, among other names, while its salts have usually been named as *azides* or *hydrazoates*.

Examples of inconsistent, incorrect, ambiguous, or careless names could be multiplied indefinitely. Mellor's remark[4] about the hydrosulfurous–hyposulfurous acid situation perhaps could apply to the field of nomenclature in general: "The arguments in favor of hydrosulphurous or hyposulphurous as a name for the acid have different weights with persons of different temperaments." Atherton Seidell (24), from the eighty-four replies to an inquiry on the reform of nomenclature sent to chemists of various countries, concluded

[3] See L. F. Audrieth, R. Steinman, and A. D. F. Toy, "Nomenclature of the Nitrogen Compounds of Phosphorus and of Sulfur," Chem. Rev. **32**, 99 (1943).

[4] J. W. Mellor, *A Comprehensive Treatise on Inorganic and Theoretical Chemistry*, Volume X, p. 166. Longmans, Green and Company, London (1930).

that "efforts to improve the nomenclature of chemistry must be confined to new names and to the harmonizing of variations in usage which do not conflict with fundamental language differences." While there can probably never be complete agreement in matters as controversial as those of chemical nomenclature, much can be accomplished in that direction. Alternative names may be allowable in certain cases, sometimes to answer very definite purposes. Resort can of course always be had to formulas when they are known. Still the goal remains a workable standardized system of nomenclature.

TABLE 8

Nomenclature of iron nitrosyl compounds

$Fe(CO)_2(NO)_2$....	Carbonyl nitrosyl	FeX_2NO	
	Nitrosyl carbonyl		
	Nitrosocarbonyl	$[NO][FeX_4]$	
		$Fe(NO)_2I$	
$Fe(NO)_4$	Tetranitrosyl	$M_2[Fe(CN)_5NO]$.	Nitroprusside
			Nitrosocyanide
		$M_3[Fe(CN)_5NO]$	
		$M_2[(ON)_4Fe_2S_2]$.....	Roussin's red salt
		$M[(ON)_7Fe_4S_3]$......	Roussin's black salt
		$[ONFeSO_4]$	
		$[4NOFe_2(SO_4)_3]$	
		$(ON)_2FeS_2$	
		$M_2[Fe(NO)_2(S_2O_3)_2]$	
		$M[Fe(NO)_2S_2O_3]$...	Thiosulfatonitrosyl
			Nitrosyl thiosulfate

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NOMENCLATURE OF THE NITROGEN COMPOUNDS OF PHOSPHORUS AND OF SULFUR[1]

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It was not until Franklin (2) had developed the nitrogen (ammonia) system of compounds that the classification of hundreds of nitrogen compounds became possible. While these can be called "ammono" and mixed "ammono aquo" compounds, such designations mean little to the average chemist despite the fact that the specialist in nitrogen chemistry finds the Franklin concept of tremendous value. However, the fundamental chemical relationships which characterize many of the compounds of nitrogen become apparent only when they are considered as "ammono" compounds. Consequently, the names of such compounds not only should take into account their chemical character, but should also be sufficiently explicit so that structure and composition are evident.

In many instances it would be unwise to propose entirely new names for compounds which are well characterized and known. When, however, the same substance has been given three or more different names, it would seem desirable to subject these to a critical examination and either to choose the one which best describes its composition, or to propose one which most nearly conforms to accepted rules of nomenclature. The present discussion is limited to the nitrogen compounds of phosphorus and of sulfur, in particular to the ammono and mixed ammono aquo acids of these elements.

A. NITROGEN COMPOUNDS OF PHOSPHORUS

A. The ammonophosphoric and ammonoaquophosphoric acids

The generic relationships which formally characterize the ammonophosphoric and the mixed ammonoaquophosphoric acids are represented diagrammatically in tables 1 and 2. For purposes of comparison the various aquo acids are also presented in table 1. Deammonation of (removal of ammonia from) $P(NH_2)_5$ leads to the various other ammonophosphoric acids and eventually to the phosphoric anammonide, P_3N_5, just as dehydration of orthophosphoric acid, either

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[1] This paper has been the subject of considerable comment and correspondence, not only prior to its presentation at the St. Louis Meeting of the American Chemical Society (April 7–11, 1941), but also subsequently by a committee of referees all of whom are recognized authorities in the field of chemical nomenclature. The recommendations here proposed represent the efforts of the authors as well as those of Professor A. M. Patterson, Dr. Janet D. Scott, and Dr. Elmer Hockett, to all of whom the original manuscript was submitted for comment. The authors consider it a privilege to acknowledge their indebtedness to these referees for their helpful suggestions.

Specific comments by the referees have been included in this paper, especially in those instances where recommendations with respect to particular compounds represent opinions by the authors and are not approved by the referees.

directly or indirectly, may give the polymetaphosphoric or the polyphosphoric acid. The ammonophosphoric acids are the nitrogen analogs of the aquophosphoric acids.

<div align="center">

TABLE 1

A. Nomenclature of the aquophosphoric acids

</div>

$P(OH)_5 \longrightarrow OP(OH)_3 \longrightarrow HOPO_2 \longrightarrow P_2O_5$

Holophosphoric*   Orthophosphoric   Metaphosphoric
acid   acid   acid

$\downarrow$ $\downarrow$

$O[PO(OH)_2]_2$† $(HPO_3)_x$†

Pyro(or di)phosphoric   (where $x = 2, 3$, etc.,
acid   the terms "dimeric",

$\downarrow$ "trimeric", or "dimer

         of", "trimer of", etc.

$PO(OH)_2$ are to be used)

O

   POOH

O

   $PO(OH)_2$

Triphosphoric acid

<div align="center">

B. Nomenclature of the ammonophosphoric acids

</div>

$P(NH_2)_5 \longrightarrow NP(NH_2)_{2,3,4,x} \longrightarrow (NPNH)_x \longrightarrow P_3N_5$

Phosphorus pentamide*   Phosphonitrilamide   Phospham   Triphosphorus
(phosphopentamide)   (phosphonitrilimide)   pentanitride
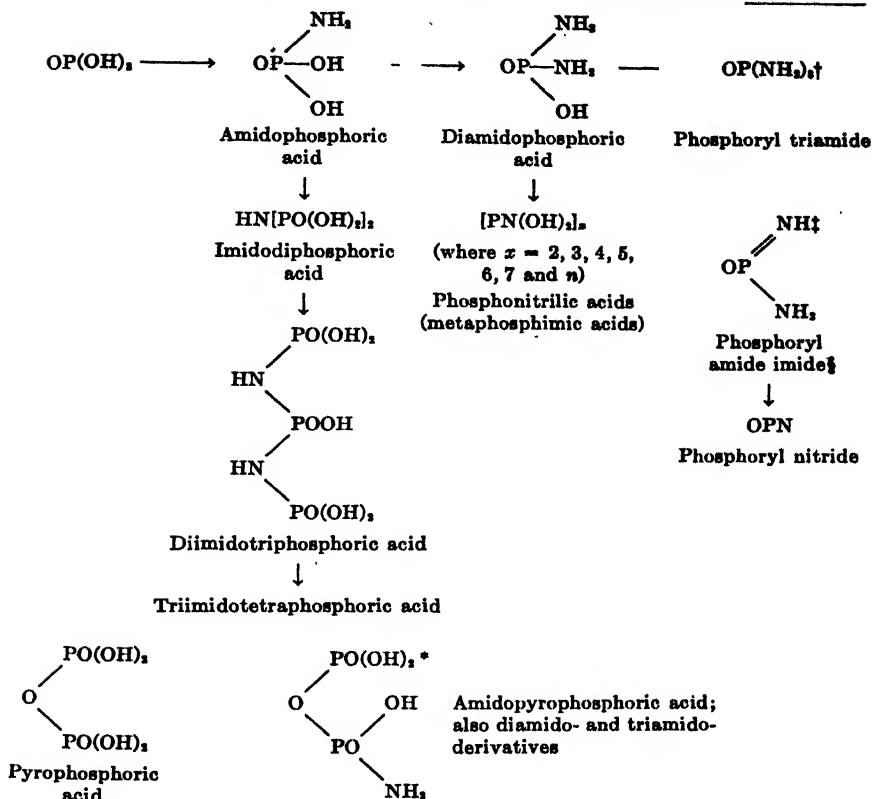
* "The prefix 'holo' for fully hydrated acids beyond the 'ortho' stage was proposed in one of the earlier papers on which the I.U.C. rules for naming inorganic compounds are based. If $P(OH)_5$ needs to be named, it can be called *holophosphoric* acid . . . then holophosphoramide can be used for $P(NH_2)_5$. Phosphopentamide is not bad. I am not sure whether I like this more or less than phosphorus pentamide."—A. M. P.

At the suggestion of J. D. S., the authors have decided to adopt the latter name.

† "It is unfortunate . . . that the same prefixes are used for the series of acids formed by loss of water and for the series of polymers of the meta acid. However, since the names for the first series conform to the International Committee Rules for indicating the number of atoms of the significant element (P) in the molecule . . . the system might as well be carried over to the aquo ammono derivatives."—J. D. S.

This difficulty is done away with by use of the system proposed by A. M. Patterson. "The prefixes di-, tri-, etc. should not be used to indicate polymeric forms. It not only conflicts with their use to indicate forms resulting from loss of water but may be misleading in other ways. It seems to me to be safer and more logical to use 'dimeric', 'trimeric', etc., or else 'dimer of', 'trimer of'. The name for $(HPO_3)_3$ would be trimeric, or trimer of, metaphosphoric acid."

TABLE 2

Nomenclature of mixed ammonoaquo derivatives of phosphoric acid

$$OP(OH)_3 \longrightarrow \begin{array}{c} NH_2 \\ | \\ OP-OH \\ | \\ OH \end{array} \quad - \longrightarrow \begin{array}{c} NH_2 \\ | \\ OP-NH_2 \\ | \\ OH \end{array} \longrightarrow \quad OP(NH_2)_3 \dagger$$

Amidophosphoric acid   Diamidophosphoric acid   Phosphoryl triamide

$$HN[PO(OH)_2]_2 \qquad\qquad [PN(OH)_2]_x$$

Imidodiphosphoric acid   (where $x = 2, 3, 4, 5, 6, 7$ and n)

Phosphonitrilic acids (metaphosphimic acids)

$$\begin{array}{c} PO(OH)_2 \\ / \\ HN \\ \backslash \\ POOH \\ / \\ HN \\ \backslash \\ PO(OH)_2 \end{array}$$

Diimidotriphosphoric acid

↓

Triimidotetraphosphoric acid

$$OP \begin{array}{c} \diagup NH\ddagger \\ \\ \diagdown NH_2 \end{array}$$

Phosphoryl amide imide§

↓

OPN

Phosphoryl nitride

$$\begin{array}{c} PO(OH)_2 \\ / \\ O \\ \backslash \\ PO(OH)_2 \end{array}$$

Pyrophosphoric acid

$$\begin{array}{c} PO(OH)_2 * \\ / \\ O \qquad OH \\ \backslash \ / \\ PO \\ | \\ NH_2 \end{array}$$

Amidopyrophosphoric acid; also diamido- and triamido- derivatives

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* The prefix *amido* here indicates that a hydroxyl group in pyrophosphoric acid has been replaced by an NH₂ group.

† *Phosphorus oxy* has been used in the past by *Chemical Abstracts* for the PO group. This terminology could be carried over to all of the compounds in the last column, *viz., phosphorus oxytriamide* for PO(NH₂)₃. The name phosphoramide has also been suggested for the latter compound (A.M.P.), but does not seem sufficiently explicit to the authors, since there are at least three amides of phosphoric acid. This suggestion meets with the approval of Janet D. Scott, who states, "Phosphoramide should denote only the completely substituted amide of phosphoric acid (just as sulfamide denotes the diamide, not the monoamide, of sulfuric acid) and therefore be explicit enough. This nomenclature corresponds with that of organic amides. However, phosphoryl triamide (or amide) seems a simpler name to figure out."

‡ It has been suggested by A. M. Patterson that the $=P\begin{array}{c}\diagup NH \\ \diagdown NH_2\end{array}$ grouping be designated the phosphamidine radical to correspond to the organic amidines. Where the two other substituents are organic radicals, this suggestion merits consideration.

§ "Phosphoryl amide imide (alphabetical order, which *Chemical Abstracts* uses with salts with two anions) seems to indicate better that both the —NH and —NH₂ groups are attached to the —PO group and not to each other."—J. D. S.

These formal analogies become a bit more complicated in the case of the mixed ammonoaquo acids. These relationships are depicted in table 2, where the gradual replacement of the OH and O groups by their isosteric ammono equivalents, the $-NH_2$ and $=NH$ (or $\equiv N$) groups, is outlined. The changes from left to right represent reactions of ammonolysis (analogous to hydrolysis), while those from the top to the bottom in each column represent reactions of deammonation.

It is proposed that the prefixes *amido* and *imido* be used generally for those derivatives of inorganic acids where the NH_2 and NH radicals replace the OH and O groups, respectively, but only in those cases where the parent substances are known to possess acidic properties in aqueous solution, or where they have been characterized in the form of salts.[2] Reference to table 2 indicates where this rule is applicable.

The compound $PO(NH_2)_3$ has been called triamidophosphoric acid. While it may have acidic character in liquid ammonia, it certainly gives no evidence of dissociating the proton in aqueous solution. Since the PO radical is known as the *phosphoryl* group, it is suggested that the compounds in the last column be called phosphoryl triamide,[3] amide imide, and nitride, respectively. In fact, there is no reason why a compound like $PO(NHC_6H_5)_3$ should not likewise be called phosphoryl trianilide.

B. The phosphonitrile radical

Difficulties arise when an attempt is made to place the nomenclature of $PNCl_2$ and its reaction products on a rational basis. Assuming that $PNCl_2$ has at least a transient existence in the monomeric form, it may be regarded as the nitrogen analog of phosphoryl trichloride, $POCl_3$. The PN radical retains its identity in all known reactions of $PNCl_2$. It is a group which corresponds to such acid radicals as sulfuryl, phosphoryl, and organic acid radicals formed from the acids by removal of OH. Most investigators have accepted the designation *phosphonitrile* for the PN group, since it is looked upon as a group resembling the CN or nitrile radical.

However, the situation is complicated by the fact that the formula $PNCl_2$ is not strictly correct, since a whole series of polymers, $(PNCl_2)_x$, where $x = 3, 4, 5, 6, 7$, and n, have been isolated and characterized. Each of these undergoes characteristic solvolytic reactions leading to well-defined derivatives,—

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[2] "Greater uniformity might be attained by the use of names that do not contain the word acid in every case in which an acid hydrogen is present. For example:

Phosphoric monoamide......... ......$OP(NH_2)(OH)_2$
Phosphoric diamide..................$OP(NH_2)_2(OH)$
Diphosphoric amide...... ....$HN[PO(OH)_2]_2$ (cf. diacetamide)."—E. H.

While such a system would lead to greater uniformity throughout the whole field of inorganic chemistry so far as the parent compounds are concerned, it would also create complications in those instances where salts of ammono acids have been isolated.

[3] "The prefix tri- for triamide is not necessary."—J. D. S. The authors feel, however, that a not too indiscriminate use of such prefixes is helpful in relating nomenclature to actual structure and composition.
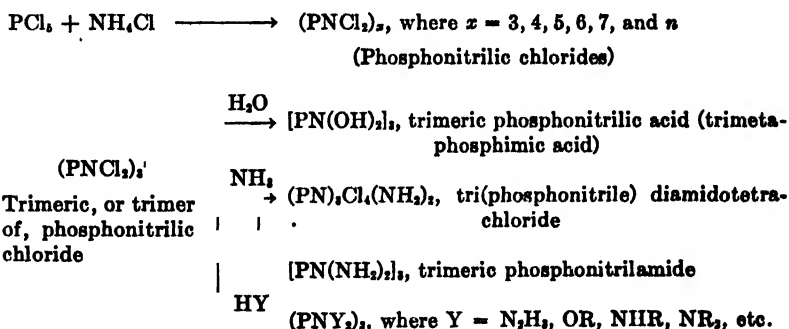
quite different from organic polymers with which the isolation of definite inter-mediates between the monomeric and the highly polymerized states is either difficult or impossible.

Some typical reactions of the trimer of $PNCl_2$ are given in table 3. Complete hydrolysis leads to the corresponding acid; complete ammonolysis to the amide. The chlorine atoms are partially or completely replaceable by reaction with hydrazine, N-substituted hydrazines, amines, alcohols, and phenols. In naming these derivatives it would seem desirable to choose a system whereby these rela-tionships are retained.

It is therefore proposed that the PN group be called the phosphonitrile radical; the acids, the phosphonitrilic acids; the amides, the phosphonitrilamides; the hydrazides, the phosphonitrilohydrazides[4]; the chlorides, the phosphonitrilic chlorides, etc. Individual members of each class of compounds can then be

TABLE 3

The phosphonitrile (PN) *radical*

$$PCl_5 + NH_4Cl \longrightarrow (PNCl_2)_x, \text{ where } x = 3, 4, 5, 6, 7, \text{ and } n$$
$$\text{(Phosphonitrilic chlorides)}$$

$$\xrightarrow{H_2O} [PN(OH)_2]_3, \text{ trimeric phosphonitrilic acid (trimeta-phosphimic acid)}$$

$(PNCl_2)_3$

Trimeric, or trimer of, phosphonitrilic chloride

$$\xrightarrow{NH_3} (PN)_3Cl_4(NH_2)_2, \text{ tri(phosphonitrile) diamidotetra-chloride}$$

$$[PN(NH_2)_2]_3, \text{ trimeric phosphonitrilamide}$$

$$\xrightarrow{HY} (PNY_2)_3, \text{ where } Y = N_2H_3, OR, NHR, NR_2, \text{ etc.}$$

* To retain the stem name phosphonitrile, this compound could be written $(PN)_3Cl_6$ and then called tri(phosphonitrile) hexachloride.

differentiated, as Dr. Patterson recommends, by using *trimer of, tetramer of,* or *trimeric, tetrameric,* etc. to specify the state of polymerization. Thus, $(PNCl_2)_3$ would be called the trimer of, or trimeric, phosphonitrilic chloride. Com-pounds such as $P_3N_3Cl_2F_4$ would require a more specific terminology. Here use can be made of the fact that the essential identity of the PN radical is re-tained by speaking of this compound as tri(phosphonitrile) dichlorotetrafluoride. In fact, this same system could be applied to other phosphonitrile derivatives, such as $(PNCl_2)_3$, which would be called tri(phosphonitrile) hexachloride. Both $[PN(NH_2)_2]_3$ and $[PN(NH_2)_2]_4$ have recently been characterized and may be designated as the trimer and the tetramer of phosphonitrilamide, respectively.

4 The authors have followed in some instances the common custom of using a connecting vowel to make for greater euphony and ease in pronunciation. However, investigators in this field, including the authors, prefer to write and speak of the halogen derivatives as the *phosphonitrilic halides,* rather than the *phosphonitrilohalides.*

It is interesting in this connection to point out that $[PN(NMg)_2]_3$ has also been reported. The name magnesium phosphonitrilamide is quite in line with our proposals.

In assigning the name phosphonitrilic to the acid formed by the hydrolysis of phosphonitrilic chlorides, the present proposal runs most seriously counter to the accepted terminology. Three structures were proposed by Stokes (3)

(1) NH_2PO_2 metaphosphamic acid

(2) $OP\diagup^{NH}_{\diagdown OH}$ metaphosphimic acid

(3) $NP(OH)_2$ phosphonitrilic acid

and were given by him what he considered appropriate names. In view of the fact that only one hydrogen atom per $PN(OH)_2$ unit could be replaced by an ordinary metallic constituent, Stokes chose to call $[PN(OH)_2]_3$ trimetaphosphimic acid.[5] While there seems little doubt that the trimeric phosphonitrilic chloride possesses structure I, the hydrolysis product is thought to undergo a tautomeric hydrogen shift from structure II to structure III.

I   II   III
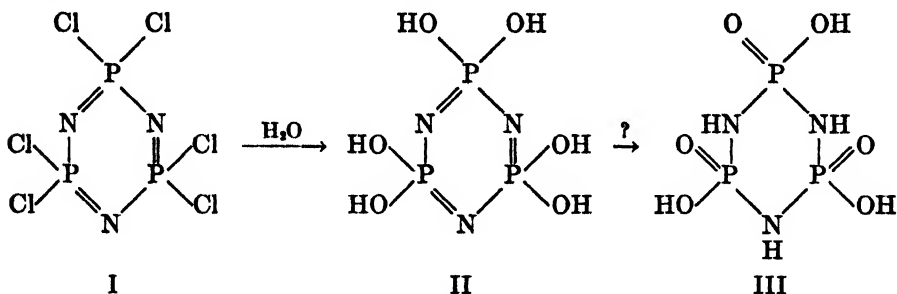
There are, however, many cases where the maximum hydrogen replacement of an acid is not attained, as, for instance, in the heteropoly and isopoly acids. Therefore, the limited experimental evidence for formula III need not weigh too heavily in the present case, especially since the use of the name metaphosphimic would hardly make apparent the chemical relationships which exist between these acids and the corresponding phosphonitrilic chlorides. Therefore, the name phosphonitrilic acid is recommended.[6]

[5] Stokes did prepare the hexasilver salt of $[PN(OH)_2]_3$, but preferred to consider it an exception.

[6] The authors prefer the system outlined in this paper for the naming of the phosphonitrile derivatives. The phosphonitrile group is a distinctive radical and the effort is made by the authors to build up a system based on this name as a group name. There is another alternative which is suggested by one of the referees (E.H.) and is extended by the others. Their comments follow:

"Nitrilophosphoric would be more nearly analogous to the names in which amido and imido are used as radical names, and would suggest more clearly that the compounds are

There is certainly no justification for speaking of the phosphonitrilic acids as phosphorus *hydroxynitrides* or *hydroxide nitrides*. One does not speak of phosphorous acid as *phosphorous hydroxide*, even though its composition is sometimes represented by the formula $P(OH)_3$.

Where compounds such as $P_4N_7Cl_9$ have been reported, but not further characterized, formulas should be used, since it is obviously impossible to assign a logical name.

C. The ammonothiophosphoric acids

Only a few representatives of a large number of hypothetical ammonothiophosphoric acids have actually been isolated. These are listed in table 4 with the suggested names.

D. Nitrogen derivatives of trivalent phosphorus

A few of these compounds are known, and these are listed in table 5. These may be looked upon as ammono or mixed ammonoaquo derivatives of phosphorous acid.

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considered as derivatives of phosphoric acid rather than as derivatives of some acid of nitrogen."—E. H.

"$PN(OH)_2$ is the stumbling block . . . but nitrilophosphoric was not considered before. The arguments for its use are good. However, nitrilophosphoric would suggest structure II (page 104). Although Webster defines nitrilo- as 'a combining form for nitrile, denoting the presence of trivalent nitrogen, $\equiv N$,' it seems strange to use it for compounds of structure III with imide groups. The authors are no doubt trying to meet a similar objection to phosphonitrilic when they say 'that the limited experimental evidence for formula III need not weigh too heavily in the present case.' If structure III is correct, an alternative name to metaphosphimic that would harmonize better with the names of the other aquo ammono acids is imidometaphosphoric (Mellor gives imidophosphoric and metaphosphimic). Perhaps it is more important to show the relationship to $(PNCl_2)_3$, as the authors maintain." —J. D. S.

"Phosphonitrile is a convenient term for the radical $=PN$, since this group does seem to preserve its identity through a series of reactions. The common name for the chlorides, phosphorus chloronitrides, is poor because the chlorine is not attached to nitrogen, and *Chemical Abstracts'* phosphorus chloride nitride is unnecessarily awkward (and the analogous name for $P_3N_3Cl_4(NH_2)_2$ would be much worse). . . . Of course, -nitrile is an unusual and therefore unfortunate ending for a radical, but I have no other to suggest except -nitrilyl. If the term phosphonitrilic acid had been introduced first, the radical should and probably would have been phosphonitrilyl. Still phosphonitrile does not seem too objectionable. . . ."—J. D. S.

"I hesitated at first about the use of 'nitrilo' . . . to denote replacement of an oxygen atom and a hydroxyl group by a nitrogen atom, but it seems to work out usefully. $NP(NH_2)_2$ would accordingly be nitrilophosphoramide and the polymeric forms would be indicated by a separate word . . . $(NPNH)_x$, or phospham, could be given a systematic name, polymeric nitrilophosphimide."—A. M. P.

"The name 'phosphonitrilyl' can conceivably be used when necessary but it is rather awkward. Is it not simpler and more consistent to use 'nitrilo' throughout? $NP(OH)_2$ would then be nitrilophosphoric acid, $NPCl_2$ nitrilophosphoryl chloride (this radical name is regularly formed so we would have to disregard the fact that 'phosphoryl' by itself means something else), . . . $NP(OC_2H_5)_2$ ethyl nitrilophosphate, etc. The higher forms would be treated as polymers without indication of structure or, where their structure is known, they might be given corresponding systematic names."—A. M. P.
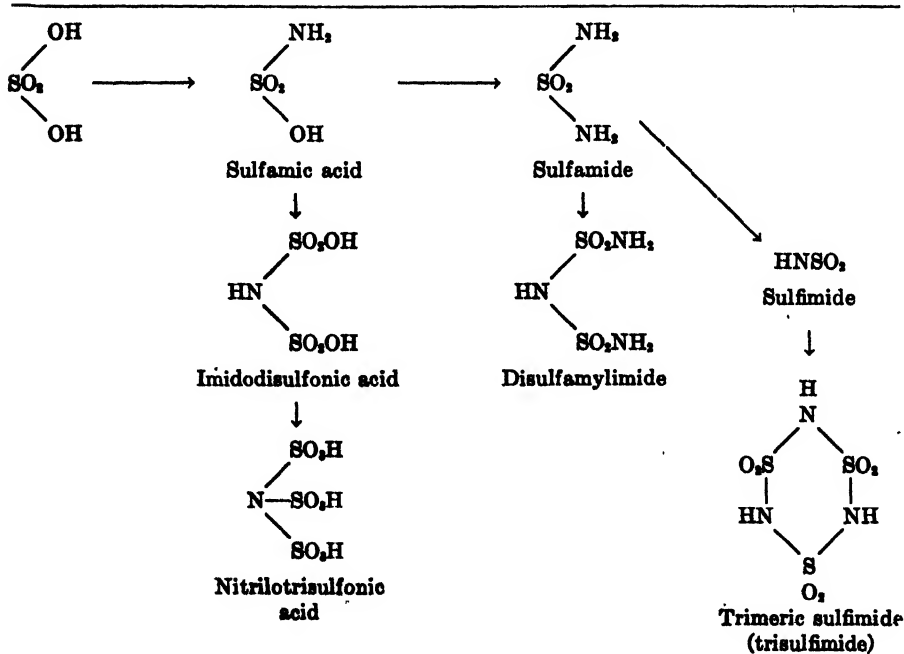
TABLE 4

Nomenclature of ammonothiophosphoric acids

FORMULA	NAME
$PS(NH_2)_3$.................	Thiophosphoryl triamide
PSN...........................	Thiophosphoryl nitride
$PN(SH)_2$...... ...._...	Dithiophosphonitrilic acid
$HNP(SH)_2$	Imidotrithiophosphoric acid

TABLE 5

Nomenclature of ammonophosphorous and ammonoaquophosphorous acids

$P(NH_2)_3$	Phosphorus triamide
$P(NH)(NH_2)$.	Phosphorus amide imide
$P_2(NH)_3$	Diphosphorus triimide
$HOP(NH_2)_2$..	Diamidophosphorous acid
$(HO)_2PNH_2$..	Amidophosphorous acid
PN...........	Phosphorus nitride
P_4N_6.	Tetraphosphorus hexanitride

TABLE 6

Nomenclature of the ammonoaquosulfuric acids

Sulfamic acid

Sulfamide

HNSO$_2$
Sulfimide

Imidodisulfonic acid

Disulfamylimide

Nitrilotrisulfonic
acid

Trimeric sulfimide
(trisulfimide)

B. THE AMMONOAQUOSULFURIC ACIDS

The derivatives of the ammonoaquosulfuric acids are quite numerous and have recently been the subject of an extensive review (1). While the terminology is not consistent, it would be inadvisable to make any major changes, owing to the fact that the parent substances and their inorganic and organic derivatives have been known under given names for many years. The chemical relationships and preferred names are given in table 6.

Originally sulfamic acid was called amidosulfonic acid. Whereas the *sulfonic* terminology was given up for sulfamic acid, it is still retained for the deammonation products of sulfamic acid. Generally speaking, it would be better to use substitutive names in inorganic chemistry (J. D. S.). On this basis sulfamic acid and its deammonation products should be called amidosulfuric, imidodisulfuric, and nitridotrisulfuric[7] acids, respectively. However, usage warrants the retention of such names as imidodisulfonic and nitrilotrisulfonic, just as *chlorosulfonic* is employed rather than *chlorosulfuric*.

If the —SO_3H grouping is to be used in an additive sense in the naming of inorganic compounds, then it might be argued that *sulfonamide* be used for the —SO_2NH_2 group in naming the compound $NH(SO_2NH_2)_2$. A difficulty arises here in that the NH_2SO_2— radical has already been called sulfamyl in compounds like NH_2SO_2Cl (sulfamyl chloride), and the latter terminology is strictly in accord with accepted rules. The compounds $SO_2(NH_2)_2$ and $NH(SO_2NH_2)_2$ are related to each other, as indicated by the following deammonation reaction:

$$2SO_2(NH_2)_2 \xrightarrow{\ -NH_3\ } NH(SO_2NH_2)_2$$

$$2SO_2(OH)_2 \xrightarrow{\ -H_2O\ } O(SO_2OH)_2$$
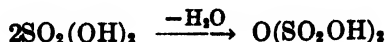
The compound $NH(SO_2NH_2)_2$ is really a deammonated sulfamide or an amide of imidodisulfonic acid (the nitrogen analog of pyrosulfuric acid). If *diacetamide* (the authors consider this a very poor name!) is acceptable for $(CH_3CO)_2NH$, the deammonation product of acetamide, then *disulfamide* might be used in this case. It seems to the authors, however, that the name disulfamylimide is generally more consistent, and it is therefore recommended for the substance which has previously been called imidodisulfamide.

The name sulfamide for $SO_2(NH_2)_2$ meets the general approval of all referees. *Sulfamide* is a contraction for *sulfuramide* or *sulfuryl diamide*, the diamide of sulfuric acid. *Sulfimide* is likewise a contraction for *sulfuryl imide*. For the trimeric form it is recommended (A.M.P.) that the designation *trimer of*, or *trimeric, sulfimide* be employed, rather than *trisulfimide*.

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[7] In view of the fact that *amido* and *imido* are accepted prefixes, then *nitrido*, rather than *nitrilo*, seems logical in those cases where the hydrogen atoms of ammonia have been replaced completely by substituents.

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THE PHOSPHONITRILIC CHLORIDES AND THEIR DERIVATIVES

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INTRODUCTION

The systematic classification and investigation of the compounds of nitrogen has been aided greatly by recognition of the fact that these substances are in many instances the nitrogen analogs of the better-known oxygen compounds. By formally setting up the so-called "nitrogen system of compounds" and proving experimentally that these compounds are related to ammonia as parent solvent in much the same way that oxygen compounds are related to water, Franklin (20) opened up a field of research which has occupied the attention of many investigators. By the use of this point of view, notable success has already been achieved in the study of sulfur–nitrogen (2a) and carbon–nitrogen compounds. Similar consideration of the many phosphorus–nitrogen compounds as ammono derivatives indicates that order can be evolved from among the bewildering maze of experimental material which has been accumulated.
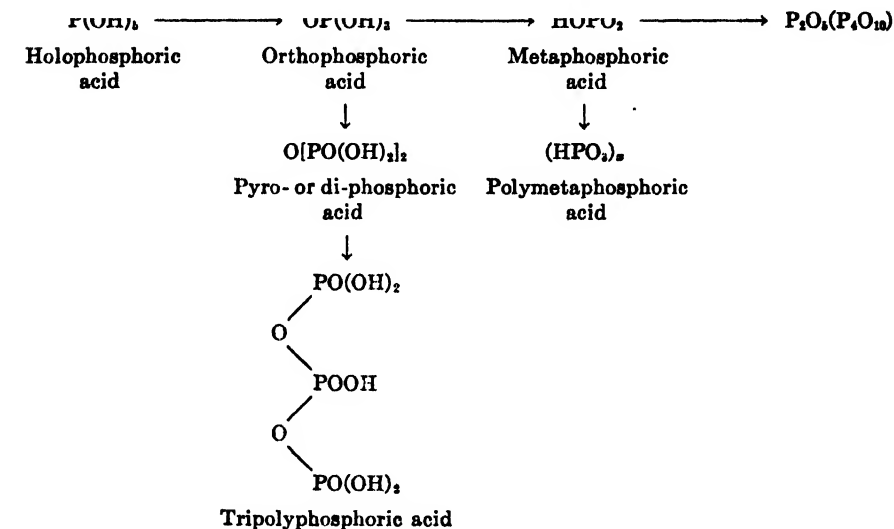
It is our purpose in this paper to discuss critically the chemistry of the phosphonitrilic chlorides. Some of these interesting substances were first obtained by Liebig (39), in an effort to prepare the amides of phosphoric acid by the action of ammonia on phosphorus pentachloride. The type formula, PNX_2, where X = halogen, reveals the fact that the phosphonitrilic halides are the nitrogen analogs of the phosphoryl halides (POX_3) and, like the latter, are acid halides capable of undergoing a wide variety of solvolytic reactions. They differ from their oxygen analogs in their ability to undergo polymerization to form products of high molecular weight resembling rubber in appearance and properties. There is no evidence that the phosphonitrilic chlorides exist as stable monomers or dimers. The lowest polyhomolog to have been isolated is the trimer, $(PNCl_2)_3$, which possesses a ring structure like that of benzene. These are but a few of the very unusual properties which have aroused current interest in the phosphonitrilic halides.

Many of the reactions and properties of the compounds under discussion will become evident from a general consideration of the nitrogen analogs of phosphoric acid in which the radicals $-NH_2$, $=NH$, and $\equiv N$ replace the isosteric radicals $-OH$ and $=O$ in the known derivatives of pentavalent phosphorus. Thus, phosphorus pentamide may be regarded as the nitrogen analog of the monohydrate of phosphoric acid, if we assume that the latter may be represented by the empirical formula $P(OH)_5$. Deammonation processes (removal of ammonia), as outlined in table 1, lead to the various ammonophosphoric acids and eventually to the phosphoric anammonide, P_3N_5, just as phosphoric acid is related by processes of dehydration, either directly or indirectly, to the polymetaphosphoric and polyphosphoric acids and to the acid anhydride P_2O_5.
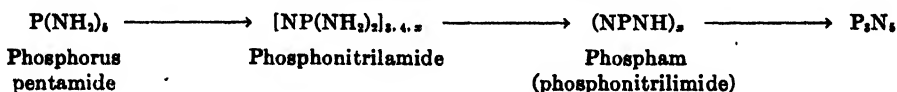
It is possible also to effect partial replacement of the aquo radicals by the corresponding nitrogen analogs to give a whole series of mixed ammonoaquo-phosphoric acids. Only a few of these are represented in table 2 and not all of these possible compounds are too well characterized. Indeed, a careful reinvestigation of these substances would seem highly desirable, since the literature contains so many conflicting statements and claims.

The problem of evaluation of the older literature is complicated by the fact that no consistent system of nomenclature has ever been employed to cover all actual

<div align="center">

TABLE 1

A. The aquophosphoric acids

</div>

$$P(OH)_5 \longrightarrow OP(OH)_3 \longrightarrow HOPO_2 \longrightarrow P_2O_5(P_4O_{10})$$

Holophosphoric acid	Orthophosphoric acid	Metaphosphoric acid

$$\downarrow \qquad\qquad \downarrow$$

O[PO(OH)$_2$]$_2$	(HPO$_3$)$_x$
Pyro- or di-phosphoric acid	Polymetaphosphoric acid

$$\downarrow$$

PO(OH)$_2$
/
O
\
POOH
/
O
\
PO(OH)$_2$

Tripolyphosphoric acid

<div align="center">

B. The ammonophosphoric acids

</div>

$$P(NH_2)_5 \longrightarrow [NP(NH_2)_2]_{3,4,x} \longrightarrow (NPNH)_x \longrightarrow P_3N_5$$

Phosphorus pentamide	Phosphonitrilamide	Phospham (phosphonitrilimide)

and hypothetical compounds. Proposals for the naming of nitrogen–phosphorus compounds have recently been made by the authors (2), in an effort to lay the groundwork for the systematization of the chemistry of these substances. The PN group is called the phosphonitrile radical, and compounds containing this combination of atoms are given this stem name where it can be shown definitely by chemical reactions that they are related. The phosphonitrilic halides are, therefore, related to the phosphonitrilamides, [PN(NH₂)₂]ₓ, and to the phosphonitrilic acids, [PN(OH)₂]ₓ, formerly called the metaphosphimic acids.

In a consideration of the chemistry of the phosphonitrilic chlorides we shall

discuss (1) the preparation, (2) the physical properties, (3) the polymerization, and (4) the chemical reactions, particularly the solvolytic reactions, which these compounds undergo.

TABLE 2

Mixed ammonoaquo derivatives of phosphoric acid

OP(OH)$_3$ $\longrightarrow$ OP(NH$_2$)(OH)$_2$ $\longrightarrow$ OP(NH$_2$)$_2$(OH) $\longrightarrow$ OP(NH$_2$)$_3$

Amidophosphoric acid — Diamidophosphoric acid — Phosphoryl triamide

↓

HN[PO(OH)$_2$]$_2$

Imidodiphosphoric acid

↓

Diimidotriphosphoric acid

↓

Triimidotetraphosphoric acid

[PN(OH)$_2$]$_x$

(where x = 2,3,4,5,6,7 and n)

Phosphonitrilic acids (metaphosphimic acids)

Phosphoryl amide imide

↓

OPN

Phosphoryl nitride (or phosphonitrilic oxide)

Amidopyrophosphoric acid; also diamido- and triamido-derivatives.

I. PREPARATION, PURIFICATION, AND SEPARATION OF PHOSPHONITRILIC CHLORIDES

A. PREPARATION

All methods for the preparation of the phosphonitrilic chlorides involve the partial ammonolysis of phosphorus pentachloride. All procedures yield mixtures of the various polyhomologs which must be subjected to subsequent separation and purification to obtain the individual members.

1. Preparation by the reaction of phosphorus pentachloride with ammonia

Justus von Liebig (39) attempted to prepare the amides of phosphoric acid by passing gaseous ammonia over phosphorus pentachloride. Instead of obtaining the expected amides, he isolated a relatively small quantity of a remarkably stable product which could be steam-distilled or boiled with acids and alkalies without undergoing appreciable decomposition. Wöhler (39) analyzed Liebig's new compound and assigned to it the formula $P_3N_2Cl_5$. Gerhardt (21, 22) and later Laurent (38) showed by analysis that the true composition may be represented by the empirical formula $PNCl_2$. On the basis of vapor-density measurements, Gladstone and Holmes (29, 30, 31) and Wichelhaus (74) proved the compound to be trimeric and assigned to it the formula $(PNCl_2)_3$.

In all of these experiments only small yields of phophonitrilic chloride were obtained. More highly ammonated products, such as phospham, are always formed even in those instances in which the pentachloride is dissslved in some non-aqueous solvent, such as carbon tetrachloride, and then treated with ammonia (47) or with ammonium carbamate (19) to moderate the reaction. It is significant, however, that small quantities of phosphonitrilic chloride are always obtained, indicating that this substance is either an intermediate or a secondary reaction product in the ammonolysis of the phosphoric halide.

$$PCl_5 + NH_3 \rightarrow \begin{bmatrix} P(NH_2)_5 \\ (PNCl_2)_x + NH_3 \end{bmatrix} \rightarrow [PN(NH_2)_2]_x \rightarrow (PNNH)_x \rightarrow P_3N_5$$
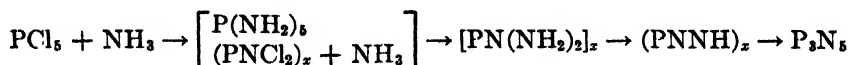
2. Preparation from phosphorus pentachloride and ammonium chloride

To prevent the formation of completely ammonated products, Stokes (64, 65, 68) used ammonium chloride as a source of ammonia.

$$PCl_5 + NH_4Cl \rightarrow PNCl_2 + 4HCl$$
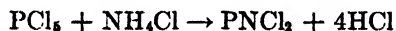
He carried out the reaction in closed tubes between 150° and 200°C. High pressures were built up, owing to formation of hydrogen chloride, and the tubes had to be opened at frequent intervals during the process in order to let the gas escape. The procedure was both costly and dangerous, in that the tubes frequently exploded. The resulting product, the weight of which was about 30 per cent of that of the original charge, consisted of a buttery mass containing crystalline material. Stokes extracted the trimer and tetramer with gasoline and fractionally recrystallized from anhydrous benzene the residue left after removal of the solvent. He verified the existence of the trimer and also isolated the tetramer, $(PNCl_2)_4$, from the benzene fraction. The pentamer, hexamer, and heptamer, together with an oily material the composition and molecular weight of which were represented by $(PNCl_2)_{11}$, were obtained from the gasoline mother liquor.

Schenck and Römer (57) were not satisfied with Stokes' method because it was dangerous, it was costly, and it produced low yields. In one of their early attempts, they heated 600 g. of phosphorus pentachloride with 150 g. of ammonium chloride in an acid-tight autoclave. They obtained their best yields at 120°C., the temperature which Stokes found to be the optimum one. The

hydrogen chloride produced as a result of the reaction was vented when it had attained a pressure of 25 atm. The heating was continued until no appreciable pressure changes were observed. About 200 g. of a crude product, contaminated with phosphorus pentachloride and ammonium chloride, was obtained. This material was subjected to fractional distillation at 2 mm. pressure. Distillation commenced at 130°C., resulting in the deposition of a white solid in the receiver, and was continued until a bath temperature of 200°C. had been attained, above which the residue in the flask foamed, then thickened, and finally assumed a dark color.

The distillate was washed with water to remove unreacted phosphorus pentachloride and then dried. This purified product, consisting of a mixture of trimer and tetramer, was then redistilled at 10 mm.; a fraction boiling at 124°C. was found to be the pure trimer, melting at 114°C. A second fraction, boiling at 185°C. and melting at 123.5°C., was found to be the pure tetramer. Both isomers were recrystallized from benzene.

The direct reaction between ammonium chloride and phosphorus pentachloride was also investigated by Besson and Rosset (4), who merely heated together a mixture of equal weights of the reactants in a retort provided with a cooling apparatus. The product which sublimed from the reaction mixture was distilled to effect separation of the trimer and tetramer. No details of the temperature or the yield were given.

This procedure has recently (63a) been studied and found to give excellent results if the proper ratio of reactants is employed and the temperature and time of heating are controlled carefully. Specific directions follow: An intimate mixture of phosphorus pentachloride (52.1 g. or 0.25 mole) and ammonium chloride (50–100 g.) is placed in the bottom of a 50-cm. Pyrex tube (50 mm. in diameter) and then covered with a capping of ammonium chloride 1 to 3 in. in thickness. The tube is immersed in an oil bath to such a depth that the ammonium chloride cap is kept largely above the liquid level. The outlet from the reaction tube is connected to a wash bottle containing sulfuric acid which serves as an indicator for the rate of evolution of hydrogen chloride. The mixture is then heated for 4 to 6 hr. at a bath temperature of 145–160°C., resulting in a conversion of 90 to 95 per cent of the phosphorus pentachloride into a mixture of the various polyhomologs of $PNCl_2$. As the reaction nears practical completion, the bubbling of hydrogen chloride through the sulfuric acid trap slows down markedly. Considerable amounts of the trimeric form sublime into the cooler portions of the reaction vessel. The residue is then extracted with low-boiling petroleum ether (50–70°C.), which removes quantitatively the trimeric and tetrameric homologs. Evaporation of the solvent yields mixtures of these corresponding quite consistently to 38 to 43 per cent of theory, based upon the amount of phosphorus pentachloride used (11–12.5 g. of the trimer–tetramer mixture, when the quantities specified above are employed). The higher polyhomologs can be obtained from the residue by extraction with benzene, carbon tetrachloride, or chloroform. Evaporation of these solutions invariably results in the formation of thick viscous oils or rubbery solids.

If the mixture of phosphorus pentachloride and ammonium chloride is heated

rapidly to red heat, small yields of the various polyhomologs can also be obtained. However, the major product appears to be phospham.

3. Preparation by the reaction of phosphorus pentachloride with ammonium chloride in the presence of an inert solvent

The yields obtained by Schenck and Römer far exceeded those reported by Stokes, but the method was not altogether satisfactory since it involved too many operations. Schenck and Römer (57) decided to carry out the reaction in an indifferent solvent in which the phosphorus pentachloride would be soluble and which would boil in the neighborhood of the most satisfactory reaction temperature. They chose s-tetrachloroethane as the solvent. Four hundred grams of phosphorus pentachloride and 120–130 g. of ammonium chloride were introduced into a liter of the solvent, and the mixture was placed in a round-bottom flask which was immersed in an oil bath. The flask was attached to a reflux condenser to the outlet of which was fitted a calcium chloride tube, in turn connected with suitable absorbents for hydrogen chloride.

The external bath was maintained at 135°C. and the mixture was refluxed for 20 hr. The major reaction was complete after 7 hr., but continued heating was necessary to drive off the dissolved hydrogen chloride. The mixture was then cooled and filtered to remove the excess ammonium chloride. After removal of the solvent by distillation at 11 mm. and 50°C., a buttery mass was again obtained, which consisted mainly of an oil suspension of crystalline material. The residue was washed with cold benzene, in which the trimer and tetramer are relatively insoluble and the higher polymers very soluble. The partially purified mixture, weighing about 100 g. and consisting of about 75 per cent trimer and 25 per cent tetramer, was then recrystallized from benzene and the purified product distilled at 10 mm. At this pressure the trimer distils at 124°C. and the tetramer at 185°C.

This procedure has since been used by all investigators with but few minor changes. Experiences by the authors (19, 62) indicate that it is advisable to remove the solvent either at as low a temperature as possible or very rapidly at temperatures of about 80°C., in order to prevent polymerization of the product, with consequent decrease in yields of the lower polyhomologs.

4. Preparation by miscellaneous reactions

The phosphonitrilic chlorides have also been obtained by the interaction of ammonobasic mercuric chloride with phosphorus pentachloride (29, 30, 31) in accordance with the equation:

$$PCl_5 + NH_2HgCl = PNCl_2 + HgCl_2 + 2HCl$$

At high temperatures (above 700°C.) nitrides of phosphorus are slowly attacked by chlorine (48, 72, 73) to give a sublimate consisting largely of the trimeric halide. Small traces of the phosphonitrilic halides are also obtained when phosphoryl nitride is treated with chlorine above 800°C. (72).

B. SEPARATION AND PURIFICATION OF THE PHOSPHONITRILIC CHLORIDES

All methods of preparation thus far devised give mixtures of various polymers of $(PNCl_2)_x$, where $x = 3, 4, 5, 6, 7$, and higher. Considerable difficulty is encountered in separating these polymers, not only because of their similarity, but because separation, if effected at higher temperature, always results in appreciable polymerization. Under any circumstances a preliminary separation of the trimer and tetramer from the remainder of the reaction product is advisable before fractional distillation, sublimation, or crystallization is attempted.

Most investigators have made use of the fact that cold benzene will extract the higher polymers ($x = 5, 6, 7$, and higher), whereas the trimer and tetramer are considerably less soluble. Such a separation is only partially successful, since considerable quantities of the lower forms go into solution, yet it was this procedure which enabled Stokes (64, 65, 68) to isolate the various polymers in the pure state. In those cases where large quantities of the higher polymers are present, the latter tend to cause formation of an extremely viscid solution in benzene which makes filtration difficult if not impossible.

The authors (62) have attempted to use a number of other solvents to effect similar separations, but only in the case of anhydrous acetic acid has any real success been achieved. The trimer and tetramer are appreciably soluble in acetic acid, whereas the higher members appear to undergo reaction and are much less soluble. Fractional crystallization from acetic acid will effect a crude separation into trimer- and tetramer-rich fractions, which can then be further purified by fractional distillation. It should be pointed out that removal of residual acetic acid is apparently necessary, since products containing traces of the acid appear to polymerize more rapidly.

If only the trimer is desired, resort can be had to a process of steam distillation (39) of the mixed product. The trimer is quite volatile in steam and is not attacked rapidly, whereas the tetramer is hydrolyzed to the corresponding phosphonitrilic acid.

After the trimer and tetramer have been separated from the higher polymers, the process of fractional distillation can be employed to obtain the pure compounds. A survey of the data in table 3, giving the melting and boiling points of the various polymers, indicates that separation of trimer from tetramer is readily effected by distillation at reduced pressure.

II. PHYSICAL PROPERTIES OF PHOSPHONITRILIC CHLORIDES

A. MELTING AND BOILING POINTS

The melting and boiling points of the phosphonitrilic chlorides are given in table 3. Those of the trimer and tetramer are known with considerable accuracy, whereas those of the higher polymers are known only approximately and have never been verified since first reported by Stokes (68).

The vapor pressure of trimeric phosphonitrilic chloride has recently (63a) been redetermined with great care over the range 75.2 to 189.3°C. For the solid–vapor curve the vapor pressure is given by the expression $\log p = -3978 \, (1/T) +$

11.187 (where t = 75.2 to 114.9); for the liquid–vapor equilibrium, log p = -2880 $(1/T)$ + 8.357 (where t = 114.9 to 189.3). On the basis of these data the triple point, representing the melting point of the trimer, corresponds to a temperature of 114.9°C. The normal boiling point obtained by extrapolation of the liquid–vapor curve to 760 mm. pressure is 252.7°C., which is somewhat lower than the previously accepted value, 256°C., reported by Stokes (68) in 1897.

The molal heat of vaporization calculated from the slope of the liquid–vapor curve is 13.2 kilocalories; the molal heat of sublimation is 18.2 kilocalories; the molal heat of fusion obtained by difference is 5.0 kilocalories.

TABLE 3

Properties of the phosphonitrilic chlorides (68)

FORMULA	SPECIFIC GRAVITY	MELTING POINT	BOILING POINTS	
			At 13 mm.	At 760 mm.
		°C.	°C.	°C.
$(PNCl_2)_3$......................	1.98 (29)	114	127	256
$(PNCl_2)_4$......................	2.18 (64)	123.5	188	328.5
$(PNCl_2)_5$......................		40.5–41	223–224.3	Polymerizes
$(PNCl_2)_6$......................		90–91	261–263	Polymerizes
$(PNCl_2)_7$......................		−18	289–294	Polymerizes

TABLE 4

Solubilities of phosphonitrilic chlorides, expressed in grams per 100 grams of solvent (16)

SOLVENT	TRIMER	TETRAMER
	grams	grams
Ether..	46.37	12.4
Dioxane..	29.55	8.23
Benzene..	55.0	21.42
Toluene..	47.3	17.8
Xylene..	38.85	13.85
Saturated petroleum hydrocarbons......................	27.9	8.39
Carbon tetrachloride.................................	38.88	16.55
Carbon disulfide....................................	52.05	22.00

It is interesting to note that the trimer and tetramer form a eutectic mixture melting at 88.5–89°C., corresponding to a trimer mole fraction between 0.6 and 0.7 (16, 19, 62).

B. SOLUBILITIES

Solubilities of the various polymers have been discussed qualitatively under their separation. Few quantitative measurements have been made and these have been collected in table 4.

The halogenated aliphatic hydrocarbons, such as chloroform, carbon tetrachloride, and s-tetrachloroethane, the aliphatic and aromatic hydrocarbons, such as petroleum ether, benzene, toluene, and xylene, and ethers, such as diethyl

ether and dioxane, may be designated as solvents in which the phosphonitrilic chlorides are soluble.   It is also reported that the trimer is soluble in phosphoryl chloride (4, 25, 49, 52), turpentine (27, 49), liquid sulfur dioxide (6, 52), and concentrated sulfuric acid (64).   Attention has already been directed to the preferential solubility of the trimer and tetramer in anhydrous acetic acid. The phosphonitrilic halides are also soluble in various alcohols, phenols, and amines, but these classes of compounds are hardly suitable solvents as some reaction always takes place, especially at higher temperatures (see section IV).

The addition of the trimer to lubricating oils, in which the compound is quite soluble, is said to reduce wear at rubbing surfaces (2b).

C. CRYSTALLOGRAPHIC FORM AND STRUCTURE

The trimer, $(PNCl_2)_3$, crystallizes in six-sided plates belonging to the rhombic system with axial ratios $a:b:c = 0.4417:1:1.8165$ (32, 75), whereas the tetramer crystallizes in the tetragonal system (35, 37).   The hexamer forms rhombic crystals with the axial ratios $a:b:c = 0.5482:1:1.1757$ (32, 71).

The trimer (35, 52) and the tetramer (35, 37) have also been subjected to x-ray studies.   These data may be summarized as follows:

	TRIMER	TETRAMER
Space group	V_H^{16}	C_{4h}^4
Dimensions of unit cell in Å.:		
a_0	14.00 (14.30)	10.82 (10.79)
b_0	6.16 (6.25)	
c_0	12.94 (13.03)	5.59 (5.93)
Molecules in unit cell	4	2
Density:		
Calculated		2.20
Found	1.98	2.18

Interatomic distances have been calculated for the tetramer (37) and are found to be (in Å. units):

(a) For bonded atoms:

        PCl_1, 1.97₅ PN, 1.66

        PCl_2, 2.01₅ PN_1, 1.69

(b) For non-bonded atoms:

        Cl_1—Cl_2, 3.17 N—Cl_2, 2.71

        P—P', 2.93 N'—Cl_1, 2.88

        N—N', 2.85 N'—Cl_2, 3.14

        N—Cl_1, 3.18

The valence angles for the various combinations of atoms are:

    P—N—P' ....123°

    N—P—N' ....117°

    Cl_1—P—Cl_2 ....105°30′

These data lead to the conclusion that the tetramer is in the form of a puckered ring.[1] In all polymers, two chlorine atoms are attached to each phosphorus atom. Resonance occurs between the two possible arrangements of the double bonds in the rings, analogous to that in aromatic compounds.

$$
\underset{\text{Trimer}}{
\begin{array}{c}
Cl_2 \\
P \\
\diagup\quad\diagdown\diagdown \\
N \qquad\quad N \\
\| \qquad\qquad | \\
Cl_2P \qquad\quad PCl_2 \\
\diagdown\qquad\diagup \\
N
\end{array}}
\qquad
\underset{\text{Tetramer}}{
\begin{array}{c}
Cl_2 \\
N{=}P{-}N \\
|\qquad\qquad\| \\
Cl_2P \qquad\quad PCl_2 \\
\|\qquad\qquad| \\
N{-}P{=}N \\
Cl_2
\end{array}}
\qquad
\underset{\text{Higher polymers}}{
\left[
\begin{array}{c}
Cl \quad Cl \quad Cl \\
\cdots{-}P{=}N{-}P{=}N{-}P{=}N{-} \\
Cl \quad\; Cl \quad\; Cl
\end{array}
\right]}
$$
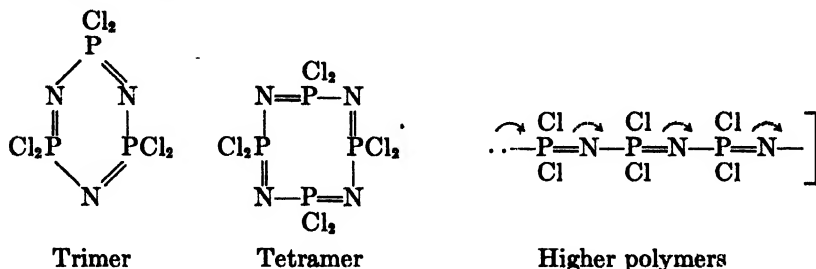
All experimental evidence points to the fact that both the trimer and the tetramer possess cyclic structures with alternate phosphorus and nitrogen atoms, whereas the higher members, including the "inorganic rubber", possess chain structures. It should be recalled that a distinct change in physical properties (see table 3) occurs in going from the tetramer to the pentamer, and also that these same lower forms exhibit marked qualitative differences in solubility from the higher polyhomologs. The trimer and the tetramer are also less easily polymerized than are the higher members, presumably because ring rupture is necessary before polymerization can occur.

D. PHYSIOLOGICAL CHARACTERISTICS

Reference has been made by many investigators (3, 39, 49) to the characteristic aromatic odor of the phosphonitrilic chlorides. If the vapor is inhaled in appreciable quantities, definite injury to the respiratory organs occurs and nausea is induced (49). Renaud (52) goes even further in emphasizing that great care should be taken in any operations involving vaporization of the phosphonitrilic chlorides. In his work on the cracking of the highly polymerized forms, Renaud mentions severe eye pains, a very general pronounced apathy, and finally difficulty in breathing, as resulting from excessive exposure to the gaseous decomposition products. These effects are not immediate and do not become apparent until several hours after exposure. Respiratory discomforts are alleviated by breathing air containing small amounts of ammonia gas.

It is interesting in this connection to report the results obtained by Dr. C. W. Kearns[2] of the Department of Entomology of the University of Illinois in a study of the pesticidal properties of the trimer. Trimeric phosphonitrilic chloride was found to be considerably more toxic to the Greenhouse Leaf Tyer than acid lead arsenate, which was used in control tests. The trimer was found

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[1] The singular stability of the tetramer seems to militate against the concept of an eight-membered ring. Copley (8) prefers to consider the polyhomologs above the trimer as having bridged or polycyclic structures with no ring containing more than six atoms.

[2] Private communication.

to have a medium lethal dosage of 0.08 mg. per gram of body weight, as compared with a dosage of 0.205 g. per gram in the case of the control agent. However, injury to foliage occurs to a marked extent, making it improbable that the phosphonitrilic chlorides will ever be of any practical value as pesticides.

III. POLYMERIZATION OF PHOSPHONITRILIC CHLORIDES

The phosphonitrilic chlorides form as complete a polyhomologous series as is known in the realm of chemistry. In addition to definite compounds the composition of which may be represented by the formulas $(PNCl_2)_x$, where $x = 3$ to 7, there have been obtained: (a) a high-molecular-weight oil, the average composition of which is represented by the formula $(PNCl_2)_{11}$; (b) gums; (c) waxes; (d) the inorganic rubber $(PNCl_2)_n$, the molecular weight of which is estimated to be at least 20,000; and (e) an infusible non-elastic material the nature of which has not yet been definitely determined.

Stokes (68) was the first investigator to show that the mixture of phosphonitrilic chlorides is converted to a rubber-like material slowly at 250°C., and very rapidly at 350°C. Short treatment of this product with benzene enabled him to extract lower polymers, while long treatment caused the rubber-like mass to swell and gelatinize. Evaporation of the benzene, however, gave back the rubber-like substance. The elastomer appears to absorb both ether and lower forms of $PNCl_2$. It is decomposed by hot water, and swells, gelatinizes, and then dissolves in warm dilute aqueous ammonia. Depolymerization begins at 350°C. and proceeds rapidly below red heat, leaving no residue if a pure substance has been used.

Renaud (50, 52) studied the polymerization of the trimer in a closed tube at 270°C. and found that liquids, gums, or insoluble or infusible products could be obtained, depending on the length of heating. He mentions the use of a trimer which had been carefully dried in order to eliminate the influence of water which, according to him, effects the polymerization process. When cooled in liquid air these products take on the aspects of a glass. A transition from the gummy form to a glass seems to occur at −47°C. Renaud assumed that the trimer on heating gives rise to chains of varying length, which are capable of enmeshing the lower polymers.

Schenck and Römer (57) studied the polymerization of the trimer and tetramer at various temperatures by placing samples in small sealed tubes and suspending these in the vapors of constant-boiling liquids. Their results are given in table 5.

Below 250°C. short heating of the trimer and the tetramer gives no polymeric material, whereas the oily polyhomologs go rapidly over to rubbery masses below 200°C. Schenck and Römer describe the inorganic polymer as an elastic and pliable material like rubber. It is colorless in the pure state and is insoluble in the usual solvents. The elastomer does swell in benzene and eventually dissolves to give a dispersion which resembles that of gelatin in water. The product is stable towards acids and alkalies, but is decomposed by long boiling with water. According to these investigators the inorganic rubber is stable in

air for a limited time only, since it loses its elasticity and decomposes to a brittle mass. Slow heating of the polymer to red heat does not bring about decomposition to lower polymers, but converts the rubbery material into a porous horny mass.

Meyer and coworkers (42, 43) produced polymers by heating either the trimer or the tetramer at 300°C. for 8 hr. In appearance these were not distinguishable from slightly vulcanized rubber. Under tension the products give fiber-like diffraction patterns in which the most probable arrangement is a succession of $PNCl_2$ units held together by primary valence forces. The elementary cell is rhombic, belonging to the C_{2v}^9 space group with the following cell dimensions: $a_0 = 11.07$ Å., $b_0 = 4.92$ Å. (fiber axis), and $c_0 = 12.72$ Å.

TABLE 5

Polymerization of the trimeric and tetrameric phosphonitrilic chlorides

NO.	LIQUID USED	BOILING POINT OF LIQUID	TIME OF HEATING	NATURE OF PRODUCT
		°C.		
1	Aniline	182	1 hr.	No change in melting point
2	Nitrobenzene	209	1 hr.	No change in melting point
3	Diphenyl	254.9	4 hr.	Turbidity in the liquid mass; when cooled gave a wax-like product with no sharp melting point; softened at 150–200°C. and was a clear liquid above 200°C.
4	Diphenyl		5 hr.	Kneadable mass which could still be melted
5	Diphenyl		6 hr.	One-piece elastic mass; did not melt; when heated to red heat gave a hard and brittle mass; longer heating did not change nature of this material
6	Phthalic anhydride	284.5	2 hr.	
7	Diphenylamine	302	1 hr.	
8		350	Few minutes	

Study of the temperature–tension curve showed the phosphonitrilic chloride polymer to be wholly analogous to rubber. When the polymer is heated at a constant degree of deformation, the tension increases to a degree which is more than proportional to the absolute temperature. It is assumed that the crystalline portions "melt" and also undergo tension. On cooling, the tension remains at first higher than in the process of heating, and decreases in an amount proportional to the temperature. The polymer then exists in an amorphous metastable state; crystallization, and restoration of the original degree of tension, occur only gradually. Contraction is produced not through intermolecular forces, but through thermal agitation of links of the flexible chain. There is a tendency to produce the preferred condition in which the chains are completely disoriented rather than the less probable oriented arrangement.

Meyer states that depolymerization of the inorganic rubber is effected at room temperature by solvents like dioxane. In many respects the behavior of the polyphosphonitrilic chloride resembles that of plastic sulfur.

Ficquelmont (14, 15) studied the behavior at room temperature of products obtained by the polymerization of $(PNCl_2)_x$ (where $x = 3$ to 7) at 350°C. If the elastomer is allowed to stand at room temperature it gradually loses its elastic properties and shows crystalline structure. This crystalline material dissolves slowly in organic solvents, such as ether and dioxane, from which some trimer and tetramer can be isolated. That this is not a depolymerization, however, is, according to Ficquelmont, indicated by the following facts: (1) The rubber-like material is not completely crystalline and the amorphous and insoluble portion can be preserved without change. (2) The crystalline material recovers its "amorphous" character by heating to 50–90°C., a temperature which corresponds to the melting range of mixtures of the lower polymers. The heat-treated material will then again slowly become partly crystalline. The rubber is, therefore, a mixture of soluble, slowly crystallizing material and an insoluble non-crystalline substance. (3) If the product is heated slowly to around 500°C., a black, insoluble, infusible, and non-elastic material is obtained. If heated rapidly, most of the elastomer distils to give a mixture of lower polymers.

Ficquelmont believes that the black infusible non-elastic product is the ultimate end product of polymerization and that the lower polyhomologs, including the elastomer, are intermediate forms. In fact, the inorganic rubber is assumed to consist of a network of highly polymerized, fibrous material, enclosing within its meshes the less highly polymerized members. This hypothesis is believed to account for its behavior on standing at ordinary temperatures and also on rapid heating.

Schmitz-Dumont (59) heated the trimer under such conditions as to cause reaction to occur in a homogeneous gas phase (1 g. of trimer sealed in a 100-cc. quartz tube and heated at 600°C.). Polymerization then takes place without the formation of the elastomer. The resulting mixture contains some unchanged trimer, some tetramer, and higher polymeric forms, both crystalline and liquid. Systems of similar components were obtained when the tetramer or the rubber-like polymer were subjected to the same conditions. It is, therefore, to be assumed that a true equilibrium exists. An increase in concentration of one of the lower polymers, or an increase in pressure, should cause a change in the quantity of higher polymers formed, an assumption which was borne out experimentally. A rise in temperature causes a decrease in the quantity of the higher polymers, indicating that the process of polymerization is an exothermic process. The higher polymers are depolymerized by heating in a vacuum at 380°C.

It is obvious from a review of the literature that various investigators are in agreement only on the conditions under which the "elastomer" is obtained (by heating to 350°C. under pressure), and that it presumably possesses a fiber-like structure. The problem is complicated by the fact that the mechanism of polymerization of the trimer and of the tetramer, both of which possess ring structures, must be different in some respects from that of the higher chain-like structures. There seems to be little question but that ring rupture is involved,

with probable formation of monomeric, dimeric, trimeric, and/or tetrameric chains of high activity.

$$(PNCl_2)_3 \rightarrow \cdots \underset{|}{\overset{Cl_2}{P}} - N - \underset{|}{\overset{Cl_2}{P}} - N - \underset{|}{\overset{Cl_2}{P}} - N \cdots \rightarrow PNCl_2 + (PNCl_2)_2 \text{ or } 3PNCl_2$$
$$\text{(ring rupture)}$$
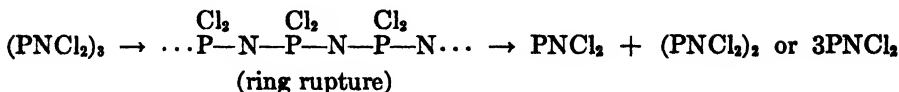
Evidence for this sort of a mechanism is only circumstantial and rests on the fact that higher polymers are obtained when the trimer is heated to temperatures above 250°C. On the other hand, the so-called inorganic rubber undergoes depolymerization in part when heated rapidly above 380°C. to give always appreciable quantities of the trimer and tetramer, as well as oily and wax-like polyhomologs. Whether the inorganic rubber contains chains of high molecular weight enmeshing lower polymers, or whether these are formed by a process of depolymerization on standing at room temperature, does not yet seem to have been established clearly.

It seems, however, that a chain mechanism is involved, but to date no investigations have been reported which give a clue as to the manner in which such a polymerization is initiated (except by heating) and continued and why it stops. One is reminded of a vinyl-type polymerization, but the formation of stable cyclic structures as intermediates has never been observed in the case of vinyl polymers. No experimental attempts have ever been made to determine if a free-radical, biradical, or chain mechanism can be applied to the polymerization of PNCl₂. In fact, it is questionable if the polymerization of PNCl₂ is quite like anything yet encountered in the realm of organic chemistry.

It is probable, however, that any polymerization involves thermal activation of terminal atoms in longer chains and ring rupture of cyclic structures. It is easier to polymerize the pentamer and higher forms than the trimer and tetramer. The fact that mixtures of various polyhomologs are always obtained indicates that such a process should be capable of a kinetic study, provided means are found for determining accurately and quantitatively one or more of the members of the series.

IV. Chemical Properties of Phosphonitrilic Chlorides

A. HYDROLYSIS

In line with their behavior as acid chlorides the phosphonitrilic halides undergo reactions of hydrolysis to yield partially and completely hydroxylated products—the latter being known as the phosphonitrilic acids (2). More vigorous reaction gives intermediate polyammonophosphoric acids (4, 49, 64, 65, 66) with phosphoric acid, hydrochloric acid, and ammonia as the end products.

$$[PNCl_2]_x \xrightarrow{(H_2O)} [PN(OH)_2]_x \xrightarrow{(H_2O)} xH_3PO_4 + xNH_3 + xHCl$$
$$\text{Phosphonitrilic acids}$$
$$\text{(metaphosphimic acids)}$$
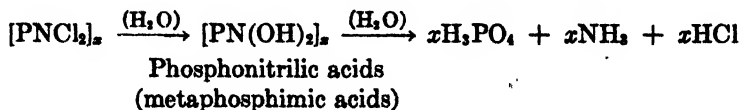
1. *Hydrolysis of trimeric phosphonitrilic chloride*

(a) *Tri(phosphonitrile) dihydroxytetrachloride*, $P_3N_3Cl_4(OH)_2$, is obtained when an ether solution of the chloride is agitated vigorously with water (49, 64, 65). The water solution contains both hydrochloric and trimeric phosphonitrilic acids, while the ether layer holds in solution the unchanged chloride and the dihydroxytetrachloride. The latter compounds are separated by extraction with benzene, in which the dihydroxy derivative is only slightly soluble. No statement can be made with respect to the location of the OH groups on the tri(phosphonitrile) ring.

The compound is rather unstable and must be considered as only one of a large number of possible intermediate products (64, 65):

$$P_3N_3Cl_6 + xH_2O \rightarrow P_3N_3Cl_{6-x}(OH)_x + xHCl$$
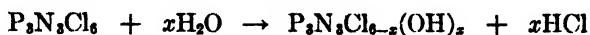
(b) *Trimeric phosphonitrilic acid*, $P_3N_3(OH)_6$ (29, 49, 58, 64, 65, 66) is an unstable compound better known in the form of its salts. The sodium salt (49, 66) can be obtained quite readily by shaking an ether solution of the chloride with an aqueous solution of sodium acetate. The reaction is slow, but complete conversion to the trisodium salt can be effected. With the exception of a tetrasodium salt (66) and a hexasilver salt (66, 69), all other derivatives are those of a tribasic acid. For this reason, Stokes (66) felt that the structure of the acid could best be represented as a cyclic imidophosphoric acid rather than as a phosphonitrilic acid.

$$(PNCl_2)_3 \longrightarrow [PN(OH)_2]_3 \qquad HN-\overset{\overset{\displaystyle O}{\|}}{P}-OH$$
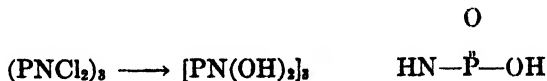
When aqueous solutions of the trimer of phosphonitrilic acid are strongly acidified, decomposition takes place to yield phosphoric acid and ammonia as end products (66). Less vigorous action leads to the formation of appreciable quantities of diimidotriphosphoric acid and imidodiphosphoric acid, both of which may be isolated in the form of their salts and both of which must be considered intermediate products of hydrolysis (66).

Diimidotriphosphoric acid

$$
\begin{array}{c}
\overset{\displaystyle O}{\underset{\displaystyle}{\parallel}} \\
P = (OH)_2 \\
HN \diagup \quad O \\
\diagdown P \diagup \!\!\!\parallel \\
\diagdown \\
(OH)_2
\end{array}
\longrightarrow H_3PO_4 + NH_3
$$
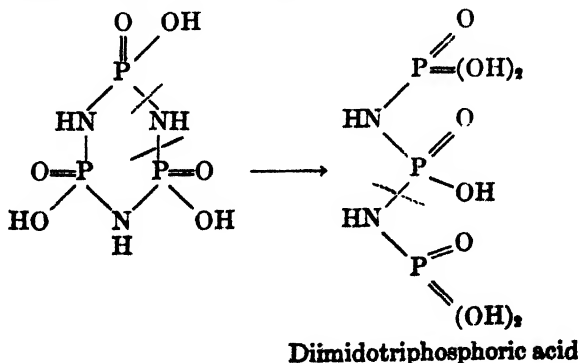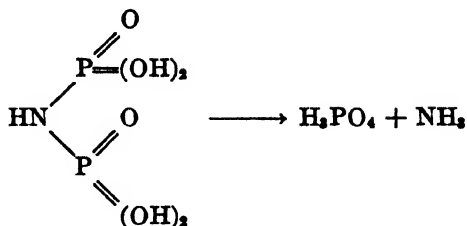
Imidodiphosphoric acid

These compounds are mixed ammonoaquophosphoric acids corresponding to tri- and di-polyphosphoric acids, respectively, and like the latter undergo hydrolytic reversion to phosphoric acid.

2. Hydrolysis of tetrameric phosphonitrilic chloride

(a) *Tetrameric phosphonitrilic acid*, $[PN(OH)_2]_4 \cdot 2H_2O$ (64, 65, 67), is an extraordinarily stable compound and is obtained by the action of water upon solutions of the tetrameric chloride in ether. It is obtained in the form of colorless needles which are but slightly soluble in cold water (0.64 g. per 100 g. of water at 20°C.). The tetrameric chloride is much more readily hydrolyzed than the trimeric compound; consequently, steam distillation has been used to effect their separation. Furthermore, the presence of the tetramer can always be detected in mixtures, owing to the fact that it hydrolyzes rapidly to give the slightly soluble acid.

Tetrameric phosphonitrilic acid is markedly resistant to the action of acids, although it will on long and vigorous action finally undergo hydrolysis to ammonia and phosphoric acid (67). Because of its unusual stability and the probable instability of the intermediate hydrolytic products, isolation of the latter has not been possible. The acid forms three series of salts in which two, four, and eight hydrogen atoms have been replaced (18, 67).

3. Phosphonitrilic acids from hydrolysis of solutions of $(PNCl_2)_3$ and $(PNCl_2)_4$ in pyridine

Schenck and Römer (57) treated solutions of the trimer and of the tetramer in pyridine with water and obtained products containing no halogen and analyzing for the pyridine salts of phosphonitrilic acids. Molecular-weight determinations were not possible, because of the insolubility of these salts in various solvents. These products lose pyridine readily in a vacuum over sulfuric acid or when heated under reduced pressure, yielding hygroscopic powders which are easily soluble in water to give acid solutions. These acids coagulate albumin, indicating that they are substances of higher molecular weight. In properties these "acids" are quite different from those prepared by other investigators.

4. Phosphonitrilic acids from hydrolysis of the higher phosphonitrilic chlorides

The higher phosphonitrilic chlorides undergo fairly rapid hydrolysis when their ethereal solutions are treated with caustic soda. Only Stokes (69, 70)

seems to have studied these higher phosphonitrilic acids, and his experimental results and analyses leave much to be desired. Stokes considered it highly probable that the pentameric and hexameric phosphonitrilic acids exist as open-chain radicals in alkaline solution and in the lactam form in neutral and acid media. Thus, the phosphonitrilic acid pentamer was represented as
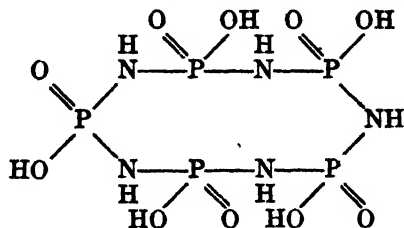
in acid solution, and as $|+ H_2O$
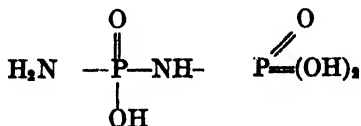
i.e., an amidotetrimidopentaphosphoric acid in the form of its salts.

While salts of the various acids have been isolated (69, 70), it should be pointed out that their composition is rather indefinite. It is interesting to note that solutions of the very unstable free acids in water can be obtained by decomposing the silver salts with hydrogen sulfide. The hydrolytic decomposition of the pentameric phosphonitrilic acid yields the tetrameric phosphonitrilic acid as one of the products (69, 70).

B. AMMONOLYSIS OF PHOSPHONITRILIC HALIDES

The action of ammonia on the phosphonitrilic halides leads to partially and completely ammonated products, the latter being known as the phosphonitrilamides. The phosphonitrilamides and their deammonation products, phospham and triphosphorus pentanitride, have been subjected to considerable study in connection with the complete ammonolysis of phosphorus pentachloride.

$$PCl_5 \xrightarrow{NH_3} P(NH_2)_5 \xrightarrow{-2NH_3} PN(NH_2)_3 \xrightarrow{-NH_3} (PNNH)_x \longrightarrow (P_3N_5)_x$$
$$(PNCl_2)_{3,4,6} \qquad \cdot [PN(NH_2)_2]_{3,4,5} \qquad [(PNNH)_x] \longrightarrow (P_3N_5)_x$$
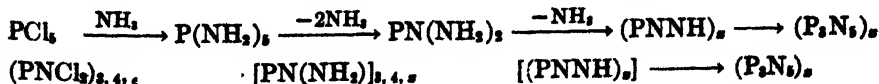
If the product of ammonolysis of phosphorus pentachloride is hydrolyzed (47), two substances are obtained, one of which is the hydrate of trimeric phosphonitrilamide, $[PN(NH_2)_2]_3 \cdot H_2O$, while the other is the tetraammonium salt of the tetrameric phosphonitrilic acid, $P_4N_4O_8H_4(NH_4)_4 \cdot 4H_2O$. It is quite probable therefore that a whole series of phosphonitrilamides, analogous to the phosphonitrilic acids, is capable of existence.

1. Ammonolysis of trimeric phosphonitrilic chloride

(a) *Tri(phosphonitrile) diamidotetrachloride*, $P_3N_3(NH_2)_2Cl_4$ (16, 44, 47, 55, 64, 65): The action of aqueous or gaseous ammonia upon an ethereal solution, or of gaseous ammonia upon a benzene solution, of the trimeric phosphonitrilic chloride yields the partially ammonated product. The compound is soluble in ether, hot benzene, and hot carbon tetrachloride, but only slightly soluble in cold benzene, cold carbon tetrachloride, and cold water. It can be recrystallized, with some decomposition, from hot water. Ficquelmont (16) gives the following quantitative solubilities of the diamidotetrachloride at 18°C. in grams per 100 g. of solvent: ether, 64.7; dioxane, 48.0; benzene, 1.55; toluene, 1.09; xylene, 0.73; petroleum ether (b.p., 80–90°C.), 0.09; carbon tetrachloride, 0.05; carbon disulfide, 0.13. The compound gives a negative chloride test in aqueous solution with silver nitrate, except on boiling. It fuses with decomposition at 162°C. and begins to lose hydrogen chloride when heated in a vacuum at 170°C. Even at 600°C. all of the chlorine is not removed; when the diamidotetrachloride is heated in a current of ammonia at 800–825°C., conversion to P_3N_5 is finally effected.

It is interesting in this connection to point out that a small quantity of this same substance $[P_3N_3(NH_2)_2Cl_4]$ was obtained as a by-product in the treatment of a cold solution of phosphorus pentachloride in carbon tetrachloride with gaseous ammonia (47). While most of the pentachloride reacted with precipitation of a mixture of the phosphonitrilamides, the carbon tetrachloride retained in solution a small quantity of $P_3N_3(NH_2)_2Cl_4$. This substance is possibly an intermediate in the ammonolysis of phosphorus pentachloride.

Hydrolysis of an ether solution of $P_3N_3(NH_2)_2Cl_4$ with an aqueous solution of sodium acetate (12) gives the trisodium salt of diimidotriphosphoric acid, rather than the trimeric phosphonitrilate.

(b) *Trimeric phosphonitrilamide*, $[PN(NH_2)_2]_3$: Liquid ammonia at first reacts quite readily (5) with the chloride, but the reaction soon slows down owing to agglomeration of the product. Only by long action (1 month to 6 weeks) in a sealed tube, carried out in such a way that the product is continually refluxed with liquid ammonia, is action completed. The amide is completely insoluble in liquid ammonia, whereas ammonium chloride is soluble. Removal of excess ammonia gives a product the composition of which corresponds to the empirical formula PN_3H_4, $[PN(NH_2)_2]$. This product is very soluble in water but can be precipitated as the monohydrate $[PN(NH_2)_2]_3 \cdot H_2O$ (47) by the addition of alcohol to the aqueous solution. When heated in a vacuum for several days at 220°C. the compound loses ammonia and the residue approaches gradually the composition of phospham, $(PNNH)_x$. Studies in this laboratory (63) indicate that this deammonation process is irreversible. Loss of ammonia is accompanied by a process involving simultaneous aggregation to give products of increasingly higher molecular weight.

A solution of $(PNCl_2)_3$ in hot benzene reacts slowly with ammonia gas to give eventually an insoluble mixture of $[PN(NH_2)_2]_3$ and ammonium chloride. An attempt to extract the ammonium chloride with methyl alcohol apparently

results in some reaction with the phosphonitrilamide. It is claimed that the two components formed are $PNNH_4OH$ and $PN(NH_2)(NHCH_3)$ in the ratio 3 moles to 10 moles (55).

When ammonia gas is passed over melted $(PNCl_2)_3$ the latter is converted into a greyish-white infusible powder approaching the composition of phospham (9, 10). It is significant that the product, even when treated in an ammonia atmosphere at 450°C., still contains from 2 to 3 per cent of chlorine (44).

2. Ammonolysis of tetrameric phosphonitrilic chloride

The action of ammonia upon an ethereal solution of $(PNCl_2)_4$ leads to progressive ammonolysis with formation of the diamidohexachloride (11), the tetra-amidotetrachloride (11, 55), and probably the tetrameric phosphonitrilamide (11, 12). A monoamido and triamido derivative are also assumed to form as intermediate products. The tetraamido compound, $P_4N_4(NH_2)_4Cl_4$ (11, 55), is assumed to decompose on heating, first with loss of hydrogen chloride to give an intermediate compound with the formula $P_4N_4(NH_2)_2(NH)_2Cl_2$ and eventually with formation of phospham.

As in the case of the trimeric halide, reaction of the tetramer with liquid ammonia is slow (47). If the reaction is allowed to take place at the boiling point of liquid ammonia, ammonolysis will occur (47). Deammonation of what is presumably the tetrameric phosphonitrilamide gives no indication of the formation of intermediate compounds (63). Deammonation at 200°C. is accompanied by aggregation to give a product which approaches the composition of phospham.

The various amides hydrolyze to give the ammonium salts of the tetrameric phosphonitrilic acid (12).

C. AMINOLYSIS OF PHOSPHONITRILIC CHLORIDES

The type reaction

$$(PNCl_2)_3 + 12RNH_2 = [PN(NHR)_2]_3 + 6RNH_2 \cdot HCl$$

has been shown to hold when the trimer and tetramer are allowed to react with such amines as *p*-toluidine, *o*-toluidine, aniline, and piperidine as well as with phenylhydrazine. It has been shown by molecular-weight determinations that the products obtained from the trimer are different from those derived from the tetramer; consequently, no depolymerization is involved in these aminolytic reactions. Table 6 gives formulas and melting points of a number of such products which may be called *N*-substituted phosphonitrilamides.

It should be pointed out that reactions of aminolysis should resemble those of ammonolysis and should give products in which only partial replacement of the chlorine has occurred. Work by Steinman (63), using such amines as cyclohexylamine, dicyclohexylamine, isobutylamine, and diethylamine, definitely indicates that complete aminolysis is difficult to attain. Lipkin (41) has recently patented a process for producing a light-colored solid, synthetic resinous material substantially insoluble in organic solvents by condensing phospho-

nitrilic chloride with butylamine and heating the condensation product to 200–400°C. under reduced pressure to effect its polymerization.

D. REACTION WITH AMINO ACID ESTERS (55)

Both the trimer and tetramer react with amino acid esters in either chloroform or benzene, giving products in which only part of the chlorine is replaced. In the case of the trimer (reaction a) only two of the six chlorine atoms are replaced, whereas four of those in the tetramer (reaction b) are presumably affected.

(a) $(PNCl_2)_3 + 4RNH_2 = P_3N_3Cl_4(NHR)_2 + 2RNH_2 \cdot HCl$
         (where RNH_2 = amino acid ester)

(b) $(PNCl_2)_4 + 8RNH_2 = P_4N_4Cl_4(NHR)_4 + 4RNH_2 \cdot HCl$

(c) $P_4N_4Cl_4(NHR)_4 + 4CH_3COCH_3 = [PNCl(NHR) \cdot CH_3COCH_3]_4$
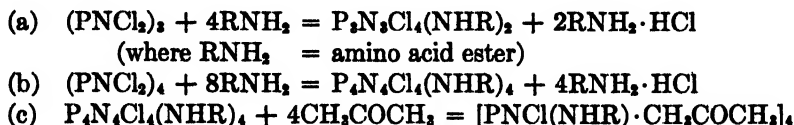
TABLE 6

N-Substituted phosphonitrilamides

FORMULA	AMINE	MELTING POINT	REFERENCES
		°C.	
$[PN(NHC_6H_4 \cdot CH_3)_2]_3$	*p*-Toluidine	243	(33, 34)
$[PN(NHC_6H_4 \cdot CH_3)_2]_3$	*o*-Toluidine	241–2	(9, 10)
$[PN(NHC_6H_5)_2]_3$	Aniline	268 (267)	(9, 10, 33, 34, 56, 57, 63)
$[PN(NHC_5H_{10})_2]_3$	Piperidine	231	(9, 10, 33, 56, 57)
$[PN(NH \cdot NHC_6H_5)_2]_3$	Phenylhydrazine	200	(9, 10, 56, 57)
$[PN(NHC_6H_5)_2]_4$	Aniline	244	(56, 57, 63)

The respective products are recovered from the reaction medium as oils. Treatment of these oils with acetone gives the crystalline acetone addition products (reaction c) in the case of the tetramer, but not for the trimer. Esters of glycolic and aspartic acids, of alanine, and of tyrosine have been found to undergo the reactions given in (a) and (b).

E. ADDITION COMPOUNDS WITH TERTIARY AMINES

The phosphonitrilic halides, like other acid halides, form addition complexes with such tertiary amines as pyridine, quinoline, and tribenzylamine (55). In view of the fact that compounds obtained from the trimer and tetramer possessed the same melting points, the assumption was made by Schäperkötter (55) that formation of these complexes results in degradation to the simple monomeric adducts: $PNCl_2 \cdot 2NR_3$. Molecular-weight determinations in camphor appear to verify this assumption. Unpublished work by Burg (6) lends credence to such an assumption, since polymerization of such addition compounds appears to proceed more rapidly.

However, the trimer and tetramer are quite soluble in pyridine and such solu-

tions have been' used for the preparation of the corresponding phosphonitrilic acids in the form of their pyridine salts (57),—and these are different! Also, the action of alcohols (75) upon pyridine solutions of the halides appears to give the respective esters of the phosphonitrilic acids.

These pyridine solutions are extraordinarily reactive. Clear solutions are obtained only in the absence of moisture, as a trace of water immediately gives a cloudy precipitate. The use of $PNCl_2$ for the purpose of drying pyridine has been suggested (57).

F. REACTION WITH ALCOHOLS, PHENOLS, AND THE RESPECTIVE THIO COMPOUNDS

It can be said with certainty that no ester of the phosphonitrilic acids has been positively identified and characterized, despite the fact that reactions of the phosphonitrilic chlorides with the alcohols have been the subject of considerable study. Wissemann (75) allowed alcohols to react either directly or in the presence of pyridine with the phosphonitrilic halides. On the basis of his observations a number of possible reactions are believed to take place:

(a) $PNCl_2 + 2ROH \longrightarrow [PN(OR)_2] + 2HCl$

(b) $PN(OR)_2 + HCl \longrightarrow NP \diagup^{OR}_{\diagdown OH} + RCl$

or

$$PNCl_2 + 2ROH \longrightarrow NP \diagup^{OR}_{\diagdown OH} + RCl + HCl$$

(c) $PN \diagup^{OH}_{\diagdown OR} + PN \diagup^{OH}_{\diagdown OR} \longrightarrow O \diagup^{PN(OR)}_{\diagdown PN(OR)} + H_2O$

or

$$PN(OR)_2 + PN(OR)_2 \longrightarrow O \diagup^{PN(OR)}_{\diagdown PN(OR)} + R_2O$$
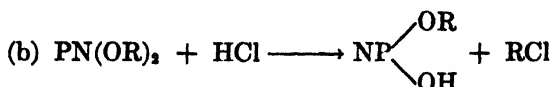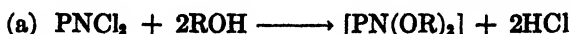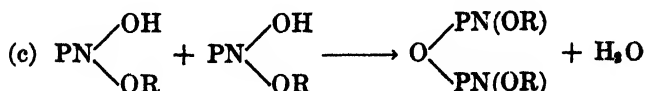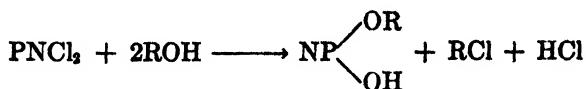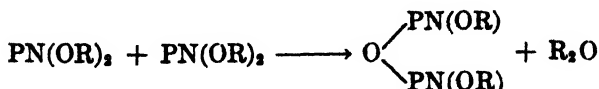
Thus, direct reaction of $(PNCl_2)_3$ with absolute methanol gives at first appreciable quantities of methyl chloride. The mixture then becomes turbid as considerable quantities of hydrogen chloride are evolved. Long heating leads to the separation of a crystalline material which, after washing with methyl alcohol and ether and drying, is shown by analysis to have the empirical composition $[PN(OH)(OCH_3)]$. Under similar conditions the tetramer yields a product the composition of which is intermediate between $[PN(OH)(OCH_3)]$ and $[PN(OCH_3)_2]$. The latter mixture is insoluble in water, whereas the substance obtained from the trimer is readily soluble.

When ethyl alcohol reacts with either the trimer or tetramer a solid product is

finally obtained which sinters between 222–225°C. and can be represented by the empirical formula:

$$O \Big\langle {{}^{PN(OC_2H_5)}_{PN(OC_2H_5)}}$$
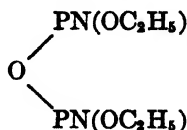
Direct reaction of benzyl alcohol gives largely benzyl chloride. Dibenzyl ether, on the other hand, reacts with either the trimer or the tetramer in accordance with the following series of equations:

$$PNCl_2 + 2C_6H_5CH_2OCH_2C_6H_5 \longrightarrow PN(OCH_2C_6H_5)_2 + 2C_6H_5CH_2Cl$$

$$2PN(OCH_2C_6H_5)_2 \longrightarrow O\Big\langle {{}^{PN(OCH_2C_6H_5)}_{PN(OCH_2C_6H_5)}} + (C_6H_5CH_2)_2O$$
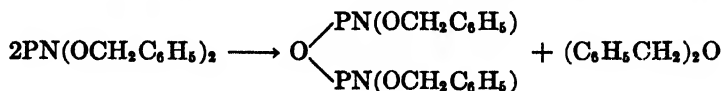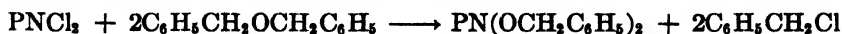
Interaction of glycerol and $(PNCl_2)_3$ in dry pyridine takes place when the solution is warmed. The precipitate so obtained is dissolved in methyl alcohol for purification, giving a product the composition of which by analysis corresponds to the formula:

$$P_3N_3Cl_2(CH_2OCHOHCH_2OH)_2(OCH_3)_2 \cdot 4C_5H_5N$$

The tetramer is much less reactive, but under the same conditions gives a compound the composition of which may be represented by the formula:

$$P_4N_4Cl_2(CH_2OCHOHCH_2OH)_4(OCH_3)_2 \cdot 4C_5H_5N$$

Interaction of $(PNCl_2)_3$ with acetoacetic ester in the presence of pyridine yields a brownish powder which is soluble in organic solvents. The compound is represented by the formula:

$$P_3N_3Cl_4(aceto)_2 \cdot 2C_5H_5N \cdot C_5H_5N \cdot HCl$$

No definite compound is obtained with the tetramer, $(PNCl_2)_4$.

From phenol (6 moles) and $(PNCl_2)_3$ (1 mole) in the presence of pyridine, Wissemann (75) claims to have obtained a greenish oil, boiling at 130–140°C. at 15 mm., the composition of which corresponds to that of an addition compound, $[PNCl_2 \cdot 2C_6H_5OH]_3$. The tetramer was found to react much less readily, giving no definite product.

With α-naphthol in the presence of pyridine a substance is obtained which, upon treatment with methanol, gives a product the composition of which may be represented by the empirical formula $[PN(OCH_3)(OC_{10}H_7)]$. Reaction with pyrogallol was also observed, but the composition of the product was not determined.

Viscous liquids of relatively high boiling points, stable towards moisture and heat, insoluble in water, but soluble in fatty oils, mineral oils, gasoline, benzene, and ether, are obtained by refluxing and treating at higher temperatures the mixed phosphonitrilic halides with metal compounds of alcohols, phenols, thiophenols, or mercaptans (40). It is claimed that such products may be

used as addition agents for lubricating oils or greases, and as plasticizers for resins, lacquers, varnishes, and rubber, and as fluid media for hydraulic brakes.

G. THE PHOSPHONITRILIC FLUORIDES (60, 61)

Experimental efforts to replace chlorine in the phosphonitrilic chlorides by fluorine have led to some rather unusual results. Interaction of ammonium fluoride with phosphorus pentachloride results in the formation of ammonium hexafluophosphate (1). Reaction of the trimer with silver fluoride under varying conditions yields products of indefinite composition. However, if lead fluoride and the trimeric chloride are heated together at temperatures between 130° and 180°C., a liquid mixture is obtained which on distillation yields a colorless distillate having a peculiar odor resembling that of hydrogen cyanide, boiling at 106°C., and melting at $-12.4°$ to $-12.1°$C. This compound was shown by analysis and molecular-weight determinations to be the tetra(phosphonitrile) dichlorohexafluoride, $P_4N_4Cl_2F_6$. In the vapor state the molecular weight decreases with rising temperature, indicating that depolymerization takes place, possibly in accordance with the equation:

$$P_4N_4Cl_2F_6 \rightarrow 2P_2N_2ClF_3$$
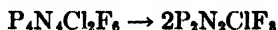
If the original material is heated in a copper bomb (for 17 hr.) at 300°C., a colorless rubber-like mass forms. This elastomer is very much less stable than the corresponding one obtained from the chlorides, since it can be completely depolymerized to give volatile products merely by heating over a low flame.

In addition to the above compound another product is obtained, boiling at 130.5°C., melting at $-25.2°$ to $-24.9°$C., and having a composition corresponding to the formula $P_4N_4Cl_4F_4$. This substance also appears to dissociate into simpler units, possibly $P_2N_2Cl_2F_2$, when heated in the vapor state to temperatures between 207° and 302°C. When the substance is heated under pressure at 300°C. an elastomer is obtained which, when decomposed at 400°C., breaks down into two liquid fractions, one boiling at 115–117°C., the other at 140–142°C. Molecular-weight determinations and analyses indicate that the first is the compound $P_3N_3Cl_2F_4$, while the second is $P_3N_3Cl_4F_2$.

If the reaction between $(PNCl_2)_3$ and PbF_2 is carried out in a glass apparatus, a crystalline product, melting at 32.5°C., is obtained, the composition of which corresponds to the formula $P_3N_3F_6 \cdot 2HF \cdot 2H_2O$. The formation of this compound is ascribed to the presence of moisture in the reaction mixture.

H. MISCELLANEOUS REACTIONS

At a temperature of 110–115°C. trimeric phosphonitrilic chloride reacts slowly with phenylmagnesium bromide in anhydrous toluene in an atmosphere of hydrogen. After purification of the hydrolyzate, a product is obtained which fuses at 230°C. and corresponds in composition and molecular weight to the hexaphenyl triphosphonitrile, $[PN(C_6H_5)_2]_3$ (53, 54). Attempts to prepare alkyl derivatives by reaction of the trimer with zinc ethyl were not successful (9, 10, 64, 65). Reaction with bromobenzene and sodium also gave no definite compound (64, 65).

Couldridge (9, 10) attempted unsuccessfully to replace chlorine in the phosphonitrilic halides by reaction with silver cyanide. Wissemann (75) claims to have prepared the pyridine and quinoline addition compounds of the phosphonitrilic cyanide by reaction of the trimer in either solvent with hydrogen cyanide.

Action of sodium, of sodium amalgam (9, 10), and of potassium (25, 27) causes decomposition. Renaud (52) found the reaction between the trimer and sodium at 120°C. to be quite vigorous. Some sodium chloride is formed, but the residual product still contains considerable chlorine.

Zinc dust reacts with the phosphonitrilic chlorides dissolved in glacial acetic acid to give some phosphine (64, 65).

The trimer of phosphonitrilic chloride also forms unstable addition compounds with sulfur trioxide and nitrogen dioxide (4). At 150°C. the sulfur trioxide compound decomposes to give chlorine, nitrogen, sulfur dioxide, thionyl chloride, and sulfuryl chloride, together with a soluble vitreous material.

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PARTIAL HYDROLYSIS PRODUCTS DERIVED FROM PROTEINS AND THEIR SIGNIFICANCE FOR PROTEIN STRUCTURE

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CONTENTS

I. INTRODUCTION

A change has come about during the past half-century in the chemical significance of the term *protein* (albumin, Eiweisskörper, etc.). While the group of substances referred to, and even their broad classification and nomenclature (*cf.* Kossel (130)), remain unchanged substantially, it is possible to define the class in a more satisfactory way. Schorlemmer (199), in 1879, writing of the "albuminous bodies" said: "All that we know of them is their percentage composition, and that they contain the carbon atoms linked together partly as in the aliphatic compounds and partly as in the aromatic bodies. We do not know their molecular weights, the most simple formula for albumin being, according to Lieberkühn, $C_{72}H_{112}N_{18}SO_{22}$ and, according to Harnack, $C_{204}H_{322}N_{52}S_2O_{66}$."

At the present day a more apt definition would be "large molecules of biological origin yielding on hydrolysis *l*-α-amino- or *l*-α-imino-carboxylic acids." This definition leaves out of account the "peptide" of *d*-glutamic acid obtained from *B. anthracis* etc. by Ivánovics and Bruckner (122), as well as the fact that a very large proportion of the proteins yield on more or less violent hydrolytic treatment a wide variety of substances not amino acid in nature. Of recent years the range of these "prosthetic groups" has been extended by the discovery that in many cases "physiologically active" small molecules (aneurin, lactoflavin, various porphyrins, chlorophyll, carotenes, etc.) occur in the living organism bound in a highly specific, if labile, manner to specific proteins. With such discoveries has come an increased appreciation of the significance and versatility of the proteins in biology, and hence an increased interest in their detailed nature.

Such remarks as the following (Pauli (174)) are not often made at the present day: "A comparatively recent epoch ascribed to the proteins the central position in the life process. Today, however, they appear rather as the passive carriers of the life phenomena, determining the important chemical and physico-chemical properties of the medium and the mechanical properties of the tissue or forming the base for certain attached active groups. The true directive participation in the maze of vital chemical reactions on the other hand devolves on scattered specific substances which, in general, belong to entirely different classes of bodies and by which the fields of the chemist and biochemist have been greatly enlarged." Bergmann (39) has dealt with the question in a manner more satisfying to modern biologists: "The major part of the organic substance of the human and animal body consists of proteins. To the proteins belong substances serving rather different biological functions, such as: hair and nails; muscle and skin tissue; tendons; egg white; the casein of milk; the fiber of natural silk; the red substance of the blood; the digestive enzymes, *pepsin* and *trypsin*; the hormone, insulin; and certain viruses. The proteins of one animal or plant species differ from those of all other species. Wherever life phenomena occur, proteins are involved in one way or another. They are, therefore, regarded as being the chemical requisite for life."

The increased precision of our chemical definition of the proteins we owe largely to the detailed evidence that has now accumulated that proteins yield on hydrolysis a limited range of chemically diverse amino acids. The history of the discovery of these in its qualitative aspects has been given by Vickery and Schmidt (230; *cf.* Dunn (60)). The quantitative aspect (amino acid analysis), in regard to both its technique and its results when applied to a number of proteins, has been reviewed by Mitchell and Hamilton (162), although a comprehensive and critical treatment of developments in this field since then has not yet appeared (*cf.* Block (46)). The present time would seem particularly opportune for such a treatment, since the application of "isotope dilution" analysis to amino acids (Rittenberg and Foster (192); *cf.* Schoenheimer *et al.* (198) for the relevant control experiments) would seem to have introduced a technical advance making possible in the future a new level of accuracy in amino acid analysis, which promises to become far more than it has been in the past a routine analytical operation.

Such a review would show that during the past fifty years sufficient proteins (e.g., clupein, wool, zein, gelatin) have had more than 90 per cent of their nitrogen accounted for as known amino acids and would justify the now widely held belief that no other type of primary hydrolysis product need contribute to the structure of a protein.

The Hofmeister–Fischer theory that proteins are built up from amino acid residues in acid–amide or "peptide" linkage with one another has remained since its formulation the basic hypothesis of protein chemistry. As Vickery and Osborne (229) put it: "Beginning with the announcement of the polypeptide hypothesis, the study of the proteins became once more an occupation in which a self-respecting organic chemist might take a part." These authors have re-

viewed the older alternative and supplementary hypotheses. Some more recent (and more speculative) views have been criticized by Pauling and Niemann (173), who conclude: "It is our opinion that the polypeptide chain structure of proteins, with hydrogen bonds and other interatomic forces (weaker than those corresponding to covalent bond formation) acting between peptide chains, parts of chains and side chains, is compatible not only with the chemical and physical properties of proteins, but also with the detailed information about molecular structure in general which has been provided by the experimental and theoretical researches of the last decade."

The main evidence in favor of the peptide hypothesis falls into the following classes: (1) Proteins yield on hydrolysis approximately equal numbers of amino and carboxyl groups simultaneously; most of the other chemical and physical properties of "intact" proteins are consistent with what would be expected from peptides of the naturally occurring amino acids. (2) Peptide-like simple substances (as well as free amino acids) occur commonly in nature, e.g., glutathione, carnosine, hippuric acid, pantothenic acid, etc. (3) Enzymes capable of splitting proteins are also capable of splitting and synthesizing peptide bonds in synthetic compounds. The establishment of the general truth of this we owe largely to Bergmann and his collaborators (for review and references see Bergmann (39)). Especially before synthetic substrates for pepsin had been discovered, this test proved an obstacle to the acceptance of the peptide hypothesis. (4) Peptides of known constitution (established by synthesis) have been shown to result from the partial hydrolysis of proteins. It is with evidence of this type and its bearing on the structure of proteins that the present review is concerned. It is hoped to establish that the comparative poverty of the data that have accumulated under this head is due more to the inadequacy of the techniques employed than to any defect in the peptide hypothesis. The newer physical methods for the characterization of proteins, combined with improved amino acid analysis, have made it possible to obtain very precise information as to the number and nature of the amino acid residues in one molecule of a "homogeneous" protein. Inside the framework of this information and the peptide hypothesis, even assuming that the molecule consists of a single *unbranched* peptide chain, the possibilities of isomerism are enormous. Thus, for a molecule containing altogether 288 amino acid residues, equally distributed between twelve different amino acid species, 0.6×10^{300} different isomers are possible. (Fischer (78)) made similar calculations, at a time when less was known of the molecular dimensions of proteins, for a triacontapeptide.) This isomerism is based on the "classical" formula alone; it is obviously extended almost beyond comprehension when the configurational isomerism postulated by Pauling (172), based on secondary valence, is taken into account. Nevertheless, taking into account only this limited isomerism of a schematized albumin molecule, it is clear that the coexistence of a single physical molecule of each isomer is impossible, since the amount of matter involved (10^{280} g.), whatever its relation to the amount of matter in the universe, exceeds the more relevant mass of the earth by a factor of 10^{253}.

Irrespective, however, of the theoretical limits to protein isomerism imposed by an *a priori* argument such as that given above, it is becoming increasingly clear as experimental data accumulate that the proteins exhibit very definite regularities of structure, even permitting in some cases, such as that of insulin (*cf.* Crowfoot and Riley (50)), the use of the concept "molecule" in the same sense as for simple organic compounds.

In the search for such structural regularities, the postulate of regular repetition of amino acid residues along a peptide chain, which appears to have been first explicitly enunciated by Kossel and Pringle (134), has achieved prominence in recent years as a result of the speculation put forward by Bergmann and Niemann (41, 42, 43). They postulate that in proteins any particular amino acid residue recurs in the unbranched peptide chain with a frequency expressible as $2^m \times 3^n$, where m and n are positive integers or zero and, further, that the number of residues of any particular amino acid occurring in one protein molecule is expressible in the same form, as is the total number of all amino acid residues in one protein molecule.

Without attempting to offer a detailed criticism of the theory here, it must be emphasized that the most important experimental evidence that has been produced in its support rests on analyses of the amino acids in complete hydrolysates of proteins. While evidence of this type is important in establishing the totals of the amino acid residues in the molecule, it is clear that the only *direct* evidence in respect of the fundamental postulate of Bergmann and Niemann, the regular recurrence of particular amino acid residues along the peptide chain, can come either from the synthesis of a protein or from the isolation of recognizable protein breakdown products. The second of these approaches seems more profitable at present than the first, and is likely to yield information about the detailed chemical structure of proteins, whatever the fate of the Bergmann–Niemann hypothesis.

Additional importance can be attached to studies of partial breakdown products of proteins, since recent serological studies (*cf.* especially Landsteiner and van der Scheer (141)) suggest that the nature of particular groupings of amino acid residues of greater or less length along a peptide chain may serve as the basis of antigenic specificity. Recently, also, Pauling (172) has formulated a theory of antibody formation and reaction in physicochemical terms. This is based on the configurations that a peptide chain can assume, and it is tentatively suggested that proline and hydroxyproline residues may play an important rôle in determining these configurations. Investigation of partial hydrolysis products of purified antibodies may in the future help to throw light on their mode of action, and on their structural relation to "normal" globulin.

It seems clear that the phenomena of biological specificity which have been studied in such detail by serological techniques are by no means restricted to serology; similar mechanisms may be postulated for enzyme action, specific permeability, reproduction, etc. and in all these fields our accumulating knowledge stresses the rôle of the proteins.

It is the purpose of the present review to enumerate comprehensively and

critically the data that have so far accumulated on the partial hydrolysis products of proteins; to assess as far as possible their significance for our present knowledge of protein structure; and to review, with an eye to future developments, the techniques that have been employed in this field, for it seems probable that in this direction at present lies the way forward towards the goal cited by Bergmann (39) as "to establish the molecular composition and architecture of the various proteins with the same precision as the molecular composition and architecture of simpler molecules have been ascertained," and thereby, one may hope, to establish with greatly increased precision the nature of living matter.

II. Significance and Authenticity of Partial Hydrolysis Products from Proteins

The present review aims at dealing comprehensively with those products that have been found to result from the partial hydrolysis of proteins. The emphasis is laid more on the chemical nature of the products studied than on the kinetics of their formation or the theoretical background that inspired their isolation. Non-isolative investigations are therefore referred to only where they seem to throw light on the phenomena under discussion. In general, compounds fall within the scope of this review when they contain two or more amino acid residues in a molecule. It is possible, especially when dealing with proteins that are not homogeneous and of which the "purity" (cf. Pirie (176)) is difficult to assess, that some of the more complex isolation products described, differing in composition from the original material, may arise less from partial hydrolysis than from a fractionation of the different constituent molecular species of the original protein material. This question becomes especially thorny in dealing with the insoluble proteins. Thus, it is generally recognized that wool, as it has usually been subjected to chemical study, consists of at least two different histological components, which have not in the past been readily separable by mechanical means. Since these (the scales and the cortical ·cells) have definitely distinct physical properties, it seems not unreasonable to expect differences of chemical composition or structure. The question whether the cortical cells of wool differ in composition from the intercellular material has been discussed by Elsworth and Phillips (62), who give references to the earlier literature. This comparatively simple case is cited as an obvious example of a phenomenon that may be expected in all the less readily fractionable protein materials. A more complex example is offered by silk fibroin, and is discussed in this connection below. For the case of casein, reference should be made to Linderstrøm-Lang's thorough investigation of its fractions (152; cf. also Holter et al. (116) on the course of peptic digestion of these fractions and for clupein the work of Felix et al. cited below). Although in most investigations there is good evidence that hydrolysis of the starting material has occurred, it will be appreciated that heterogeneity of the starting material cannot fail to make interpretations of structure more equivocal than they otherwise would be.

Up to this point it has been a tacit assumption that the isolation of compounds

of two or more amino acid residues and more or less understood constitution is to be taken as evidence for the preëxistence of these groupings in the intact protein. The *a priori* nature of this assumption should be noted. The recent discovery of Behrens and Bergmann (38) that papain is capable of carrying out synthesis and hydrolysis of peptide bonds simultaneously in the same reaction mixture casts doubt at least on the significance of products obtained from proteins through the action of papain. Other enzymes also must be under suspicion, and the whole question of the significance of products of enzyme action must be treated with reserve until the specificity of enzymes in proteolysis has been more adequately established. The researches of Bergmann and his collaborators (*cf.* Bergmann (39)), using synthetic substrates, have taken us a long step in this direction.

With non-enzymic hydrolytic agents, the only established synthetic action seems to be the formation of diketopiperazines from dipeptides etc. on heating with acids or water. High temperatures seem to favor ring formation, which does not appear to take place in concentrated acids at low temperatures (*cf.* Abderhalden and Funk (17) and Abderhalden and Komm (22, 23)). Hopkins (117) noted hydrolysis and diketopiperazine formation on boiling glutathione with water. Synthesis from free amino acids treated with acid or alkali has never been found in numerous control experiments. It seems therefore legitimate to regard products isolated from partial acid or alkali protein hydrolysates as of significance in establishing protein structure until contrary evidence is produced. It is satisfactory that in the past protein chemists, in studies of this sort, have more often employed partial acid hydrolysis than enzymic hydrolysis.

Attention must also be paid to artifacts arising in the course of isolation of the hydrolysis products. Although the balance of evidence suggests that diketopiperazines found in protein hydrolysates are not preformed in proteins (this whole question and Abderhalden's diketopiperazine theory of protein structure are dealt with in detail by Vickery and Osborne (229)), it seems likely that these compounds arise by secondary condensation of amino acid residues already linked to each other by one bond. This is, in fact, the basis of Fischer and Abderhalden's (80, 81, 82) esterification method of separating dipeptides from higher peptides and free amino acids. Nevertheless, free amino acids under certain conditions can and do condense to form diketopiperazines,—e.g., upon distillation of their esters (Fischer) or when simply heated, especially with alcohols, or under dehydrating conditions. Thus Dakin's isoleucine valine anhydride from casein (52) and hydroxyproline proline anhydride from gelatin (53) were obtained only after prolonged refluxing of free amino acid mixtures in butyl alcohol, and must be regarded as artifacts (*cf.* Osborne, Leavenworth and Nolan (171)).

It is obvious that the *yield* of any particular partial hydrolysis product is of fundamental importance in any interpretation of protein structure. Workers in this field have in many cases entirely omitted reference to yields, thus robbing their work of most of any value that it otherwise might have. In the present review special emphasis is placed on yield, which is noted wherever possible.

These yields should be studied in connection with tables of the amino acid composition of proteins, to be found in reference works such as those of Mitchell and Hamilton (162), Jordan Lloyd and Shore (126), etc. It should be noted that in nearly every case the isolation of any particular partial hydrolysis product must have been accompanied by considerable losses. Rittenberg and Foster's isotope dilution method (192) seems likely to prove itself of incalculable value in this field.

With regard to the authenticity of partial hydrolysis products of proteins, it would clearly be desirable to apply the same criteria as those applied to the naturally occurring amino acids by Vickery and Schmidt (230). These are: (1) In order that an amino acid shall be accepted as a definite product of the hydrolysis of proteins, it must also have been isolated by some worker other than its discoverer. (2) Its constitution must have been established by synthesis and by demonstration of identity between the synthetic product and the racemized natural product, or by actual resolution of the synthetic product and preparation of the optically active natural isomer. If these criteria are adopted, remarkably few of the partial hydrolysis products of proteins described below could be called authentic, since of the minority the constitution of which has been established by synthesis, few would conform to criterion 1.

It should be noted that synthesis in this field is very laborious, although the carbobenzoxy technique of Bergmann and collaborators marks a big step forward towards its standardization. In general, it is necessary that the synthetic product should be made directly from optically active amino acids, since any simple peptide containing n amino acid residues has 2^n optical stereoisomers, a mixture of which in unknown proportions arises when synthesis is carried through using racemic amino acids as starting material. The whole problem is complicated by the fact that the methods employed in isolating the natural product often lead to its partial racemization.

It seems true that polypeptides as a class do not crystallize at all well. Organic chemists in the past have attached an almost fetish-like significance to crystallinity, and it seems opportune to point out that, in comparing synthetic with natural products, crystal form and melting point are not the only criteria that can be used.

In characterizing a partial hydrolysis product of a protein, an essential criterion is a quantitative analysis of the amino acids resulting on total hydrolysis. This information is of value even where (as in the phosphopeptone of Damodaran and Ramachandran (57)) too many amino acid residues are present for an immediate synthetic approach. A complete amino acid analysis of any partial hydrolysis product isolated should in general be technically easier than the analysis of the original protein. Far too many workers in this field have been content with the inconclusive data of elementary analysis.

In these more complicated cases, various methods of analytic elucidation of structure are available. These are discussed in a subsequent section of this review. Some of them have been employed in attempts to elucidate the structure of intact proteins directly; in this field, beyond the general conclusion that

amino acid side chains in most cases react as though they were free, not much of significance has been established; Gurin and Clarke (109), however, have shown by benzenesulfonylation and subsequent acid hydrolysis that a large proportion of the ε-amino groups of the lysine residues of gelatin are free, thus confirming the negative evidence obtained by previous workers who had failed to isolate lysine from hydrolysates of proteins that had been deaminated with nitrous acid. Hess and Sullivan (114) have obtained evidence of this sort for free cystine amino groups in a number of proteins, and Jensen and Evans (123) have obtained positive evidence for free phenylalanine amino groups in insulin. Dirr and Felix's (58) demonstration of a free arginine carboxyl group in clupein should also be noted.

Finally, mention must be made of the interesting, if not directly interpretable in terms of structure, studies of Dakin and collaborators (51, 54, 55) on the racemization of amino acid residues in proteins by the action of dilute alkali. In the cases of duck and hen egg albumins, which, though serologically distinguishable, do not show significant differences in amino acid composition, Dakin and Dale observed significant differences in the degree of racemization of histidine, leucine, and aspartic acid. The model experiments on peptides of the simpler monoamino acids carried out subsequently by Levene and his collaborators have tended to confirm Dakin's view that amino acid residues having a free —NH₂ or —COOH group escape racemization, but it is probable that in the case of the proteins other more complicated factors are involved.

III. Details of Investigations of Particular Proteins

A. Silk Fibroin

In addition to being the first protein material from which peptides of known constitution were isolated, this group of arthropod proteins, for which the amino acid analysis suggests a relatively simple structure, has been more closely investigated by methods of partial hydrolysis than any other group of proteins.[1]

Fischer (76), in 1902, delivered a lecture at Karlsbad in which he described how he and Bergell had isolated from a hydrolysate of silk fibroin, prepared by the successive action of hydrochloric acid, trypsin, and baryta, a dipeptide as its naphthalenesulfonyl derivative, which was thought to be glycylalanine: "Diese Beobachtung ist, wie leicht ersichtlich, von allgemeiner Bedeutung, weil sie die Möglichkeit beweist, kristallisierbare Produkte zu gewinnen, die zwischen den Peptonen und Aminosäuren stehen."

Fischer and Bergell subsequently (84) announced that they had prepared synthetically the naphthalenesulfonyl derivative of l-alanylglycine and of glycyl-l-alanine, and found neither to correspond exactly in properties with the material of natural origin, which they suggested might be a mixture of the two compounds in question. Further, there were difficulties in repeating exactly the original preparation. However, Fischer and Abderhalden (81) made use of their method

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[1] In the following, "silk fibroin" or "fibroin" refers to material from *Bombyx mori*, unless otherwise specified.

(80) of converting dipeptides to diketopiperazines through their esters. In this way they succeeded in isolating from digests of silk fibroin (prepared with sulfuric acid followed by trypsin, or by hydrochloric acid alone) crystalline glycine *l*-alanine anhydride, which they identified completely with the synthetic product. In the case of the hydrochloric acid hydrolysate, the weight of diketopiperazine isolated amounted to 12 per cent of the weight of fibroin used. Glycyl-*l*-alanine or *l*-alanylglycine could both act as precursors of the anhydride; its formation from free amino acids in the course of esterification was excluded by control experiments. The authors inclined to the view that the anhydride was formed from glycyl-*l*-alanine since, unlike the material in the digest, *l*-alanylglycine was readily split by the tryptic preparation used by them. They noted further the isolation of a small amount of glycine tyrosine anhydride. In a subsequent paper by Fischer and Abderhalden (82) this product, obtained from hydrochloric acid digest of silk fibroin (in the mother liquors from the glycine-*l*-alanine anhydride), was formally identified with glycine *l*-tyrosine anhydride obtained synthetically. The yield on one occasion was 4.2 per cent of the fibroin used, but on a second only 0.18 per cent.

In a further paper, Fischer and Abderhalden (83) returned to the original approach of Fischer and Bergell; they treated a partial hydrochloric acid hydrolysate of fibroin with phosphotungstic acid. From the syrupy material not precipitated by this reagent they isolated, by naphthalenesulfonylation, an amount of naphthalenesulfonylglycyl-*l*-alanine (formally identified with synthetic material) equivalent, as glycylalanine, to 6 per cent of the fibroin used in the preparation. As a further proof of structure it was shown that acid hydrolysis of this compound yielded naphthalenesulfonylglycine. By using esterification instead of naphthalenesulfonylation, large quantities of glycine *l*-alanine anhydride were obtained, together with smaller amounts of glycine *l*-tyrosine anhydride. In the mother liquors was also found a small amount of material having the elementary composition of alanine serine anhydride, which was not further characterized.

From the phosphotungstic acid precipitate they isolated, by fractional precipitation with alcohol, a non-crystalline material which appeared to be a tetrapeptide containing 2 molecules of glycine, 1 molecule of alanine, and 1 molecule of tyrosine. On partial hydrolysis, followed by esterification, some glycine *l*-alanine anhydride and glycine *l*-tyrosine anhydride were obtained. Subsequently, Fischer (77) prepared by synthesis one of the possible isomers of this tetrapeptide —glycyl-*l*-alanylglycyl-*l*-tyrosine—which proved to be non-crystalline and in other ways very similar to the material from silk, although it was less readily precipitated by ammonium sulfate.

Abderhalden (2) obtained from a digest of silk fibroin (70 per cent sulfuric acid for 4 days at 18°C.) 0.4 per cent of glycyl-*l*-tyrosine by direct crystallization with alcohol after removal of the sulfuric acid. Later (3) better yields (4 to 5 per cent) were obtained, together with 3.8 per cent of *l*-alanylglycine, which was adequately characterized and compared with synthetic material. Still later (4) 8 per cent of *l*-alanylglycine was found to result from a partial hydrolysis of

fibroin, carried out in Hofmann-La Roche's Basel factory, and detailed directions for the preparation were given.

Abderhalden and Suwa (35) applied the diketopiperazine procedure to partial acid hydrolysates of various silks. From Canton silk they obtained 2 to 5 per cent of glycine *l*-alanine anhydride and 1 to 3 per cent of glycine *l*-tyrosine anhydride, whereas New-Chwang silk gave 6 per cent of *l*-alanine anhydride, together with small amounts of glycine *l*-alanine anhydride. Indian tussore silk gave 2 to 5 per cent of *l*-alanine anhydride.

Abderhalden (5, 6) obtained various yields of *l*-alanylglycine from partial acid hydrolysates of Canton and Bengal silks. He consistently obtained in the mother liquors an amorphous material, which was purified by precipitation with phosphotungstic acid, followed by fractionation with alcohol. The final product was microcrystalline; on one occasion 5.6 g. was obtained from 3 kg. of fibroin. It yielded on complete hydrolysis equimolecular amounts of glycine, *l*-alanine, and *l*-tyrosine, and had the molecular weight of the corresponding tripeptide. It agreed in properties with synthetic *l*-alanylglycyl-*l*-tyrosine, although the synthetic material had a rather lower rotation and was completely amorphous. This may have been due to partial racemization in the course of synthesis. Naphthalenesulfonylation followed by acid hydrolysis resulted in glycine, naphthalenesulfonylalanine, and *o*-naphthalenesulfonyltyrosine, although the yields were very poor. A similar investigation of "silk peptone" by Abderhalden and Funk (18) had led to poor yields of acylated products.

After the war, Abderhalden (7; *cf.* 8) returned to the study of the hydrolysis products of silk fibroin and reported, in addition to a new amino acid analysis, the isolation of 5 per cent of glycine *l*-alanine anhydride from a partial acid hydrolysate, together with glycine *l*-tyrosine anhydride and a product giving on complete hydrolysis serine, glycine, and alanine. Later (10) he obtained 8.5 per cent of glycine *l*-alanine anhydride from a partial hydrolysate with sulfuric acid ("silk peptone").

Abderhalden and Stix (33) attempted, without reaching any definite conclusion, to allocate the free amino groups of "silk·peptone" by coupling with dinitrophenyl chloride, followed by acid hydrolysis. The same authors (34) studied the results of reducing "silk peptone" with sodium in amyl alcohol, and obtained piperazines (unidentified). Abderhalden and Schwab (28) claimed to have identified in this material, using ethyl alcohol for the reduction, piperazines in unspecified yield corresponding to glycine alanine anhydride, alanine serine anhydride, and an "anhydride of glycylalanylglycyltyrosine." Only incomplete elementary analyses of the hydrochlorides of the bases were given, and no comparisons were made with synthetic material. The further claim was made, based on equally inadequate evidence, to have isolated the precursors of the two last-mentioned piperazines directly from a preparation of "silk peptone." The importance of these results for Abderhalden's diketopiperazine theory of protein structure has been stressed by Vickery and Osborne (229).

Abderhalden and Heyns (19) subjected tussore silk to partial acid hydrolysis, and obtained 0.28 per cent of *l*-alanyl-*l*-tyrosine, from which a dibenzoyl deriva-

tive was obtained which yielded on acid hydrolysis tyrosine, benzoic acid, and benzoylalanine. The material was satisfactorily identified with the synthetic peptide. A portion of the silk which had not readily dissolved in the 70 per cent sulfuric acid used for the hydrolysis yielded a product which was thought to be alanylalanylalanylglycine. It had approximately 25 per cent of its nitrogen as amino nitrogen, and on complete hydrolysis followed by benzoylation it yielded 3 molecules of benzoylalanine and 1 molecule of hippuric acid; on benzoylation followed by acid hydrolysis, benzoylalanine was obtained. Successive condensation with benzylamine, acid hydrolysis, and condensation with phenyl isocyanate (cf. Abderhalden and Brockman (16)) yielded the phenylureido compound of glycine benzylamide; this was regarded as demonstrating that the free carboxyl group of the peptide belonged to its glycine residue.

These experiments, together with Abderhalden and Suwa's isolation of alanine anhydride from tussore silk, suggest that this material has a very different structure from that of *Bombyx mori* fibroin, from which no product suggesting the direct linkage of alanine with alanine or tyrosine has yet been isolated.

Goldschmidt, Martin, and Heidinger (98; cf. Goldschmidt and Strauss (99)) reported the isolation from fibroin after treatment with alkaline hypobromite of an insoluble product giving on hydrolysis only glycine and alanine in the molecular ratio 1:3. This product, representing a considerable proportion of the weight of fibroin used, was reported to give the same x-ray diffraction spacings as the original fibroin.

In a further paper (Goldschmidt, Freyss, and Strauss (97)), the degradation of fibroin by 5 N hydrochloric acid at 25°C. was studied. After 80 to 160 hr. about half the nitrogen in solution was amino nitrogen, but insoluble material equivalent to about 30 per cent of the original fibroin remained. This gave on complete hydrolysis 20–32 per cent of glycine, 57–68 per cent of alanine, and 6–11 per cent of tyrosine. It was claimed that no other amino acids were present, and it was suggested that the material consisted of alanine, glycine, and tyrosine in the molecular ratio 13:8:1. X-ray powder photographs of the material revealed the main spacings present in untreated silk fibroin. In none of these studies by Goldschmidt and collaborators can the chemical identification of alanine be regarded as satisfactory.

Uchino (225) has made a comparative study of the partial degradation of silk fibroin by various methods. Upon heating glycerol at 180–190°C. partial solution resulted, giving a 2.5 per cent yield of glycine alanine anhydride. Sulfuric acid (100 per cent) in the cold effected very little degradation to products of low molecular weight. Hydrolysis with dilute acid in the autoclave led to liberation of 35–48 per cent of the nitrogen of the fibroin as amino nitrogen. No further increase in this value occurred on prolonging the treatment, but the biuret reaction became progressively weaker and disappeared. This was attributed to simultaneous anhydrization of dipeptides and hydrolysis of higher peptides, giving no net change of amino nitrogen. Dilute alkali in the autoclave gave no such limiting value to the ratio of amino nitrogen to total nitrogen. Among the better characterized products obtained from the dilute acid hy-

drolysates by direct crystallization and by extraction with organic solvents were glycine alanine anhydride and glycine tyrosine anhydride. A nitrogen balance was constructed for the various fractions obtained, and the distribution of glycine, alanine, and tyrosine in the fractions was studied. It was noted that partial hydrolysis products of silk fibroin lost amino nitrogen on heating with glycerol at 170°C.

Grant and Lewis (104) repeated and confirmed Abderhalden and Steinbeck's (32) preparation of "silk peptone". This material had 17–64 per cent of its nitrogen in the form of amino nitrogen, and its tyrosine content was not significantly different from that of the original silk fibroin. Much shorter treatment of the fibroin (1 hr.) with 70 per cent sulfuric acid at 30°C. resulted, however, in a water-insoluble fraction (22–40 per cent of the weight of the fibroin used), having 1.7–3.0 per cent of its nitrogen in the form of amino nitrogen, and 6.4–8.0 per cent as tyrosine nitrogen; from the mother liquors of this a fraction was obtained by alcohol precipitation (10–27 per cent of the weight of fibroin used), having 10–17 per cent of its nitrogen as amino nitrogen and only 1.0–2.3 per cent as tyrosine nitrogen. Similar divergences in the tyrosine content of fractions from silk fibroin are indicated by Kaneko and Komatsu (127).

Although they do not constitute a rigid refutation, it is difficult to see how Grant and Lewis' results can be reconciled with Bergmann and Niemann's (43) theory of the structure of silk fibroin, which demands that every second, fourth, and sixteenth consecutive residue of the peptide chain shall be respectively glycine, alanine, and tyrosine. Similarly, the materials isolated by Abderhalden and Bahn, though obtained in small yield and not finally identified, were definitely more deficient in glycine and alanine, and in one case richer in tyrosine, than any product that could be expected to result from hydrolytic breakdown of the structure postulated by Bergmann and Niemann. The results of Goldschmidt and collaborators raise further difficulties. Moreover, difficulty has been experienced by those who have studied fibroin by the methods of x-ray diffraction in correlating the unit cell weight with the chemical data, and workers in this field (cf. Bergmann and Niemann's paper for references) have been inclined to regard silk fibroin as composed of "crystallites" embedded in an "encrusting material" of different composition.

It appears, moreover, that there is a mistake in Bergmann and Niemann's calculations. In the paper in question, they state: "The mean molecular weight of the amino acids formed by the complete hydrolysis of fibroin was estimated to be 102, which in turn leads to a value of 84 for the average residue weight." The accompanying calculation (table 1) is based on the values for glycine, alanine, tyrosine, arginine, lysine, and histidine employed by Bergmann and Niemann, supplemented by the figures of Abderhalden (7) for leucine, phenylalanine, proline, and serine. The figures in brackets incorporate estimates of the serine and threonine content of silk fibroin obtained by the use of periodic acid (Martin and Synge (158, 159)). Assuming that silk fibroin contains 18.5 per cent of nitrogen, it is seen that the amino acid values employed in the calculation, including the newer values for serine and threonine, account for 90 per cent of

the nitrogen of fibroin. By dividing the total of column 1 by the total of column 3 the average molecular weight of the determined amino acids of fibroin is found to be 90.0 (92.2), leading to an average residue weight of 72 (74.2). This is significantly different from the value 84 used by Bergmann and Niemann, and implies that the glycine residues have a frequency not of 2 but of 2.38 (2.31); the frequency of the other residues must be altered in the same proportion.

Recently, Meyer et al. (160) have criticized Bergmann's figure for the tyrosine of silk fibroin, and have proposed a lower figure. They found no alteration in the tyrosine content of the residue from partial dispersion of fibroin in lithium bromide solution. They regard the fact that there is no change in the x-ray photograph given by fibroin when it is coupled with diazobenzenesulfonic acid

TABLE 1
Amino acid composition of silk fibroin

AMINO ACID	(1) WEIGHT	(2) MOLECULAR WEIGHT	(3) GRAM-MOLECULES PER 100 G. OF PROTEIN	(4) GRAMS OF NITROGEN PER 100 G. OF PROTEIN
	per cent			
Glycine...............	43.8	75	0.5840	8.18
Alanine..............	26.4	89	0.2966	4.15
Tyrosine..............	13.2	181	0.0729	1.02
Arginine....	0.95	174	0.0055	0.31
Lysine....	0.25	146	0.0017	0.05
Histidine.............	0.07	155	0.0005	0.02
Leucine........	2.5	131	0.0191	0.27
Phenylalanine.	1.5	165	0.0091	0.13
Proline..............	1.0	115	0.0087	0.12
Serine......	1.8 (17.4)	105	0.0171 (0.1655)	(2.32)
Threonine............	(1.0)	119	(0.0084)	(0.12)
Total.......	91.47 (108.07)		1.0152 (1.1720)	(16.69)

as evidence for the absence of tyrosine from the "crystallites" responsible for the photograph.

In spite, therefore, of the fact that the best-characterized partial hydrolysis products of fibroin, often isolated in quite significant yields, are entirely consistent with Bergmann and Niemann's theory of its structure, it seems that the theory will have to be substantially modified, very probably in the direction of recognizing microheterogeneity in silk fibroin.

B. PROTAMINES AND HISTONES

After silk fibroin, the group of basic proteins (protamines) derived from the ripe sperm of certain fish has probably received the closest investigation by the methods of partial hydrolysis. The complete literature on these substances and the related "histones" up to 1927 was surveyed by Albrecht Kossel (131),

who had himself inspired most of the experimental work. Of the protamines, clupein and salmine have received most attention. Their amino acid composition is very simple, there being present in a complete hydrolysate 2 molecules of arginine to 1 molecule of monoamino acids. No basic amino acids other than arginine are present.

Kossel (133), in 1898, wrote: "Erhitzt man die Protamine mit verdünnter Schwefelsäure zum Sieden, so entstehen zuerst Produkte welche ihnen hinsichtlich ihrer Eigenschaften noch nahestehen und welche man als Peptone der Protamine—'Protone'—zu betrachten hat; aus diesen gehen dann durch weitere Zersetzung die Basen hervor. . . ."

These "protones" were recognized as having sulfates more soluble in water than those of the original protamines, and to be in general less readily precipitable, e.g., by proteins.

About the same time, Kossel and Mathews (133) studied the action of proteolytic enzymes on the protamines, and obtained from sturine, by the action of a tryptic preparation, a basic material giving a crystalline double salt with silver nitrate. Its elementary composition suggested that it might be formed from 1 molecule of histidine and 2 molecules of lysine minus 1 molecule of water, but the amount of material available was insufficient for further investigation.

Goto (101) extended the work on "protone". He prepared a copper salt from the material from clupein, studied the optical rotation, and measured the molecular weight cryoscopically and ebullioscopically. This was found to be 384–443. As pointed out by Dakin and West (56), these results are certainly low, as such results always are for chain molecules except in the most dilute solution. An experimental study of the deviations in molecular-weight determinations on chain molecules of known molecular weight and constitution has been made by Meyer and Lühdemann (161). Goto also prepared double salts of "clupeone" with platinum chloride. Arginine determinations showed no significant differences from those carried out on the original clupein.

Kossel and Dakin (132) obtained a "protone" by the action of intestinal mucosa extract for 18 months on clupein sulfate. This was separated from the ornithine, urea, monoamino acids etc. simultaneously formed by silver–baryta precipitation. The material proved different from Goto's product, having only 69.7 per cent of its nitrogen as arginine nitrogen. Complete acid hydrolysis yielded ornithine, which was identified as its phenylhydantoin. Similar observations on material prepared from clupein by partial alkaline hydrolysis were made by Kossel and Weiss (137) and extended to gelatin (138).

Kossel and Pringle (134) described further work with "clupeone". The material was fractionated by precipitation with excess picric acid in neutral and acid solution, by precipitation with silver–baryta, and as its copper salt. None of the various fractions had an arginine content significantly different from that of the original clupein. The monoamino acid fraction from a complete hydrolysate of one of these preparations of "clupeone" was found to consist of a mixture of proline with other amino acids.

Thus so far, no partial hydrolysis product of clupein had yet been demon-

strated to be significantly different in amino acid composition from the original substance, and Kossel and Pringle inclined to the view that clupein consists of a regular arrangement of arginine (a) and monoamino acid residues (m) along a peptide chain, thus:

—aamaamaamaamaamaamaamaamaam—

Kossel and Weiss (136) obtained a crystalline picrolonate from a partial acid hydrolysate of clupein. This material was converted to the corresponding hydrochloride, and fractionated by precipitation with alcohol, and with phosphotungstic acid. The arginine content of some of the resulting fractions was a little lower than that of the original clupein. The same material (Hirayama (115)) yielded a crystalline naphthalenesulfonyl derivative, containing 3.9 naphthalenesulfonyl residues per nine nitrogen atoms. Clupein, naphthalenesulfonylated under the same conditions, took up only 1.3 residues per nine nitrogen atoms, although benzenesulfonylation introduced 2.4 residues per nine nitrogen atoms.

Nelson-Gerhardt (166) obtained evidence (from molecular-weight determinations, and from increase of formol titration on further hydrolysis with acid) for the occurrence of peptides consisting entirely of monoamino acids in a partial acid hydrolysate of salmine. The protamine was hydrolyzed with 6 per cent sulfuric acid at 140°C. for 2 hr., and the resulting solution was freed from arginine and arginine peptides by the silver–baryta procedure before investigation. Such peptides could not be expected on the basis of Kossel and Pringle's view of the structure of clupein and salmine.

Gross (107), working with clupein, confirmed Nelson-Gerhardt's results, and also obtained evidence for the occurrence of arginine peptides under the same conditions of hydrolysis. The material obtained from the hydrolysate by silver–baryta precipitation was fractionated by precipitation with phosphotungstic acid in 33 per cent alcohol. In this way amorphous material was obtained containing only about 3 per cent of its nitrogen in the form of amino nitrogen (Van Slyke). Twenty grams of clupein gave 125 mg. of nitrogen in this form (after analytical samples had been removed). In a molecular-weight determination, the material did not raise the boiling point of water. On total hydrolysis, 23.8 per cent of the nitrogen was found to be amino nitrogen and 96 per cent of the nitrogen was precipitable by silver–baryta, and was identified as arginine. Gross suggested that the material was either a peptide consisting entirely of arginine residues (eight or more) or else arginine anhydride. He established that free arginine did not polymerize on autoclaving with dilute sulfuric acid.

All the partial acid hydrolyses of protamines described above were carried out with dilute acid at high temperatures: Kossel and Staudt (135) hydrolyzed clupein with 70 per cent sulfuric acid at 37°C. for several days, and obtained a basic material (precipitated as an oil with flavianic acid in unspecified yield) which gave only arginine on complete hydrolysis, and which, on the basis of amino nitrogen and molecular-weight determinations, they concluded was

arginylarginine contaminated with a little free arginine.   It could not be identified with the (unhydrolyzable) "arginylarginine" of Fischer and Suzuki (89), the non-peptide structure of which was later established by Bergmann and Zervas (44) (*cf.* Edlbacher and Bonem (61)).   Kossel and Staudt's product was amorphous, and they could prepare no crystalline derivatives from it.

All the work on protamines described above was carried out by Kossel and his school.   Since Kossel's death, the most important work of this character on protamines has been that of Felix and collaborators.

Felix and Dirr (67) fractionated clupein methyl ester hydrochloride (prepared without apparent degradation by using methyl alcoholic hydrogen chloride) and obtained preparations of widely differing methoxyl content (0.76–3.20 per cent), which suggested that clupein is a heterogeneous material.   Dirr and Felix (59) repeated the work of Kossel and Staudt on the isolation of arginylarginine from clupein.   Starting with 50 g. of the (unfractionated) methyl ester hydrochloride, they obtained 5 g. of crystalline arginylarginine dipicrate.   The actual quantity of arginylarginine in the hydrolysate was estimated (by the amount of oily flavianate precipitated) as equivalent to 45 per cent of the arginine in the clupein used.   The arginylarginine was further converted to its amorphous methyl and ethyl ester hydrochlorides, which appeared to retain excess of alcohol.   Unlike Kossel and Staudt's preparation, that of Dirr and Felix gave no biuret reaction.

Felix, Inouye and Dirr (72) investigated the products of the action of trypsinkinase on clupein B (*cf.* Felix and Dirr (67)).   By fractionation with alcohol, methyl alcoholic hydrogen chloride, picric acid, and flavianic acid the following products were obtained: (*1*) A dipeptide of arginine and serine in the form of a crystalline picrate (1 g. of picrate from 30 g. of clupein methyl ester hydrochloride).   This had the correct elementary composition and amino nitrogen content, and on hydrolysis yielded equimolecular quantities of arginine and serine. (*2*) A dipeptide of arginine and alanine as its crystalline picrate (1.5 g. of picrate from 30 g. of ester hydrochloride), which was characterized in the same way as the previous compound.   (*3*) Three and a half grams of arginylarginine dipicrate (*cf.* Dirr and Felix (59)) from 64 g. of ester hydrochloride.   (*4*) A dipeptide of arginine and hydroxyproline as a crystalline flavianate (1 g. of flavianate from 64 g. of ester hydrochloride).   This gave the expected quantity of arginine on acid hydrolysis, and hydroxyproline was also isolated.   Since the dipeptide had a free amino group, it was assigned the structure arginylhydroxyproline. (*5*) Two grams (from 64 g. of ester hydrochloride) of the crystalline flavianate of a dipeptide of arginine and valine.   Valine was formally identified in an acid hydrolysate.

Although the constitution of none of the above products was established by synthesis, the evidence that they are dipeptides of the stated amino acids can be regarded as satisfactory.   Considerable losses were obviously inherent in the methods used for their isolation.

Felix, Hirohata, and Dirr (71) studied the hydrolysis of clupein by boiling 2 *N* hydrochloric acid.   Study of the liberation of urea by arginase at pH 8

and pH 9.3 after different times of hydrolysis led to no very definite results. This was an attempt (*cf.* Felix, Dirr, and Hoff (68)) to discriminate between free arginine and arginine in peptide linkage having its carboxyl free. From a 16-hr. hydrolysate, arginylarginine was obtained as its dipicrate, and it was found also to form a crystalline dipicrolonate. From an 8-hr. hydrolysate of 50 g. of clupein ester hydrochloride were obtained: (*1*) Two and six-tenths grams of the crystalline picrolonate of what appeared to be a tripeptide containing 2 molecules of arginine and 1 molecule of a monoamino acid having perhaps a five-carbon-atom skeleton. This picrolonate was possibly the same as Kossel and Weiss' (136) product, as it had the same melting point (*cf.* Hirayama (115)). (*2*) Five and eight-tenths grams of the crystalline picrolonate of a substance having 6.7 per cent of its nitrogen in the form of amino nitrogen, and giving a positive biuret reaction. Acid hydrolysis resulted only in arginine. The substance gave a crystalline picrate. It appeared to be arginylarginylarginylarginine. Attempts to prepare its hydrochloride led to rupture of the molecule.

Felix and Mager (74) slightly modified the methyl ester fractionation of clupein, and conducted an amino acid analysis on the clupein C fraction obtained in this way. A small amount of hydroxyproline was found in the monoamino acid fraction, and it was concluded that the molecule contained 2 molecules of serine, 2 molecules of alanine, 4 molecules of (proline + hydroxyproline), 3 molecules of valine, and 22 molecules of arginine. Since no free amino group exists in clupein, although formol-titratable nitrogen was found (*cf.* Sørensen (216) for the formol-titration behavior of proline), it was concluded that the terminal residue of the peptide chain was prolyl or hydroxyprolyl, and the formula

$$m'aaaammaaaammaaaammaaaammaaaammaa$$
$$NH\dots\dots\dots\dots\dots\dots\dots\dots\dots\dots\dots\dots\dots COOH$$
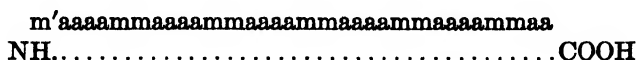
where   m′ = proline or hydroxyproline residue,

     m = monoamino acid residue (including proline and hydroxyproline), and

     a = arginine residue,

was given as being consistent with all the partial hydrolysis products isolated from clupein as well as with Gross' and Nelson-Gerhardt's demonstrations of the presence of peptides of monoamino acids.

Studies of the enzymic hydrolysis of protamines have also been made by Takemura (223), Rogozinski (193), Felix and Lang (73), and Waldschmidt-Leitz *et al.* (231, 232, 233, 234). None of the partial hydrolysis products obtained in these studies was subjected to complete amino acid analysis. Waldschmidt-Leitz (231) gives a review of the work of his school on the protamines.

The partial hydrolysis of calf thymus histone has also been investigated. On digestion of this material with pepsin hydrochloride Kossel and Pringle (134) obtained a product which they named "histopeptone". This was isolated from the neutralized digest by precipitation with sodium picrate, and could further

be precipitated with silver–baryta. Sixteen and five-tenths grams of histopeptone sulfate were obtained from 80 g. of the air-dry histone. The histopeptone had a higher nitrogen content than the original histone, and gave no ammonia on acid hydrolysis. On total acid hydrolysis, the histidine and lysine contents of the histopeptone were found to be about twice those of the original histone. Only 27 per cent of the nitrogen of the hydrolysate was not precipitable by phosphotungstic acid. The mother liquors from the preparation of the histopeptone yielded a fraction richer in monoamino acids than the original histone.

Felix (64) confirmed Kossel's work on the histopeptone from thymus. Of the nitrogen of the histone 30.1 per cent was obtained as histopeptone, which gave on hydrolysis the same base and monoamino acid figures as those found by Kossel. Attempts at fractionation by silver–baryta precipitation at different pH's suggested that the material was homogeneous.

C. PARTIAL HYDROLYSIS PRODUCTS CONTAINING BASIC AMINO ACIDS DERIVED FROM OTHER PROTEINS: THE "KYRINE" QUESTION

Siegfried (200) reported investigations of the hydrolysis of gelatin (and "gelatin peptone") by 12.5 per cent hydrochloric acid at 38°C. The optical rotation of the hydrolysate was found to be constant after 120 hr. Precipitation with phosphotungstic acid gave 12 g. of basic material from 400 g. of gelatin. In working up the material, considerable losses were encouraged, in order to achieve fractionation. The platinum salt was employed for this purpose. A number of preparations of the sulfate of the base were analyzed, and were in agreement with the formula $(C_{21}H_{39}N_9O_8)_2(H_2SO_4)_5$. The base formed a crystalline phosphotungstate. "Für die das Sulfat bildende Base schlage ich den Namen *Kyrin* vor (τὸ κῦρος, der Kern einer Sache im bildlichen Sinne) und zwar für die aus Glutin entstehende Base den Namen *Glutokyrin*." Naphthalenesulfonylation gave a crystalline product, incorporating five naphthalenesulfonyl groups per "molecule" (21 carbon atoms) of base. Acid hydrolysis with hydrochloric acid gave a little ammonia, with sulfuric acid none; two-thirds of the nitrogen was precipitated by phosphotungstic acid after acid hydrolysis. This appeared to consist of equimolecular amounts of arginine and lysine. Histidine was absent. From the phosphotungstic acid filtrate, glutamic acid was isolated, and was thought to account for about one-third of the nitrogen present in this. The rest was thought to be glycine. It was shown that a complex of 1 molecule of arginine + 1 molecule of lysine + 1 molecule of glutamic acid + 2 molecules of glycine − 4 molecules of water agreed with the elementary composition of the material. Siegfried summed up as follows: "Wenn sich entsprechende nicht basische Komplexe auffinden lassen, die ähnliche Widerstandskraft gegen Hydrolyse besitzen, wird man diese neben dem Kyrin zu ordnen haben. Zerfällt aber das Proteinmolekül bei der Reaktion, bei welcher das Kyrin erhalten bleibt, in Kyrin und die einfachen, letzten Spaltungsprodukte, die Amidosäure etc., so wird dem basischen Kern, dem Kyrin, eine Sonderstellung zuzuweisen sein, in diesem Falle wird es *der* Kern sein."

Later Siegfried (201) reported a more detailed investigation of the mono-

amino acid fraction of "glutokyrin". Much less glutamic acid than the "theoretical" was obtained. After removal of this, glycine in unspecified yield was formally identified. At the same time (202) he described the preparation of a similar "kyrine" from casein, and noted that fibrin also yielded a "kyrine". In the case of casein, a rather more complex series of precipitations was found necessary. Free proline was isolated in the course of the preparation. Eventually the "kyrine" was obtained as its sulfate, to which the formula $C_{28}H_{47}N_9O_8 \cdot 3H_2SO_4$ was assigned on the basis of elementary composition. The yield was not specified. The material gave no ammonia on acid hydrolysis, and was free from histidine. From 84 to 85 per cent of the nitrogen of its acid hydrolysate was precipitable by phosphotungstic acid; this was made up of approximately 2 molecules of lysine to 1 molecule of arginine. In the monoamino acid fraction arginine was isolated, though in low yield. The composition 2 molecules of lysine + 1 molecule of arginine + 1 molecule of glutamic acid was tentatively assigned to the "kyrine". The material was optically inactive. Both the material from casein and that from gelatin gave a biuret reaction.

Skraup and Zwerger (214) criticized Siegfried's work, asserting that free lysine, arginine, and histidine were present in the product. They characterized the lysine as its picrate and as its platinum double salt. Since, however, they had used for the hydrolysis concentrated hydrochloric acid for 42 hr. at 100°C., conditions usually reckoned to give complete hydrolysis, little weight can be attached to this criticism. Later Skraup and Witt (212) repeated Siegfried's work on casein, using the same conditions of hydrolysis as Siegfried. It was found that little fractionation resulted from the precipitation of "kyrine sulfate" with alcohol; fractionation with phosphotungstic acid, potassium mercuric iodide, and picric acid led, however, to fractions of differing elementary composition, and evidence was obtained that these fractions had different contents of basic amino acids.

Siegfried (203) replied to the criticisms of Skraup and Zwerger, and gave further details of the properties of the phosphotungstates and picrates of "caseinokyrine". He gave details of the elementary composition of "fibrinokyrine", which became constant after nine reprecipitations of the sulfate. No yields were stated. In a further paper (204) he described the application of the phosphotungstic acid fractionation of Skraup and Witt to "caseinokyrine"; he was unable in this way to alter its elementary composition. By applying his carbamino reaction to "caseinokyrine" and "fibrinokyrine", he found that the intact "kyrines" reacted with smaller proportions of carbon dioxide than did their hydrolysates. This was taken as further evidence of the complex character of the "kyrines".

Levene and Birchard (148) repeated the work of Siegfried with gelatin employing the amino nitrogen determination of Van Slyke. A qualitative examination of the hydrolysis products of the "kyrine" showed that arginine, lysine, and glutamic acid were definitely present, probably also proline and perhaps glycine and alanine. The amino nitrogen content of the "kyrine" before hydrolysis was 32 per cent of the total nitrogen, rising to 65 per cent

afterwards. It was thus impossible that the "kyrine" was a homogeneous penta-peptide. On "purification" with silver–baryta, there was found in the precipi-table fraction what appeared on similar evidence to be a dipeptide of arginine and glutamic acid. However, the ratio of amino nitrogen to total nitrogen in the filtrate from this rose from 23 per cent to 36 per cent on further treatment (five times) with silver–baryta, suggesting that the product was not homogeneous.

Levene and van der Scheer (150) also investigated the "kyrine" from casein. After fractionation with silver–baryta, the fractions were further fractionated with phosphotungstic acid in the hot and in the cold. In one of the four resulting fractions there was obtained an unspecified yield of a substance showing a tendency to crystallize. Its amino nitrogen before hydrolysis was 50 per cent of the total nitrogen, rising to 75 per cent after hydrolysis. Lysine was the only basic hydrolysis product; in addition to this there appeared to be an amino acid and an imino acid present. The elementary composition agreed with that of a tripeptide of lysine, valine, and hydroxyproline. A little valine, but no hydroxyproline, was obtained from the hydrolysate. The possibility of other lysine peptides of similar make-up being present was not excluded.

Siegfried (205) applied the silver–baryta precipitation to "glutokyrine" and investigated the fractions by carbamino and formol titrations. Results similar to those of Levene were obtained, and no satisfactory evidence was obtained that the silver–baryta precipitation induces breakage of peptide bonds (cf. Todorowic (224)). Siegfried and Schunke (207) investigated the question further, and obtained evidence from the Van Slyke and carbamino figures, though not from the formol titration, suggesting that hydrolysis might be effected by the silver–baryta treatment. Baryta alone did not appear to effect this. The naphthalenesulfonylation of "kyrine" was also studied.

Luck (156), in an investigation of the origin of the ammonia liberated by casein on acid hydrolysis, found that about one-third of this was not liberated by tryptic digestion. Isolative investigations suggested that this trypsin-resistant ammonia precursor in the digest yielded largely glutamic acid, lysine, and ammonia on acid hydrolysis. Naphthalenesulfonylation before hydrolysis led to the isolation of what was probably dinaphthalenesulfonyllysine, and the product (40 g. from 1200 g. of casein) may have been very impure lysylgluta-mine. Such a compound might clearly, in its deamidated condition, be a con-stituent of Siegfried's "caseinokyrine".

Haurowitz (110) studied the partial hydrolysis of globin by acid. A prepara-tion was made in the same way as Kirbach's "kyrine" (128), and was shown by silver–baryta precipitation not to be homogeneous. The course of hydrolysis of globin by 70 per cent sulfuric acid at 40°C. was studied by formol titration. By precipitation with mercuric sulfate from a 3-day hydrolysate, followed by reprecipitation with silver–baryta, followed by alcohol precipitation, 6.76 g. of material was obtained from 165 g. of horse hemoglobin. Free amino acids and diketopiperazines were shown to be absent from this preparation, and it was further tested for homogeneity by electrodialysis and by fractional precipitation

with silver–baryta. Hydrolysis gave 69 per cent of the total nitrogen as histidine, and 31 per cent as monoamino acid nitrogen (of which proline was 17.8 per cent and tyrosine 0.3 per cent). Amino nitrogen (Van Slyke) was 18 per cent of total nitrogen before hydrolysis, and 51 per cent after hydrolysis. Proline was demonstrated in the hydrolysate through its hydantoin. An ester distillation of the monoamino acid fraction suggested that mainly leucine was also present. The material was not split by the enzymes with which it was tested.

Haurowitz's work confirms an earlier report by Abderhalden (1) of the isolation of material rich in histidine and leucine from a partial acid hydrolysate of hemoglobin by precipitation with mercury. Abderhalden gave no experimental details.

Grassmann and Lang (105) reinvestigated "glutokyrine". They confirmed most of the earlier work, although they could not detect glutamic acid among its hydrolysis products. A little glycine was isolated as its ester hydrochloride. Determinations of amino nitrogen and esterification experiments suggested that the material is a mixture of di- and tri-peptides of basic amino acids. Hydrolysis after deamination with nitrous acid gave no lysine, but the yield of arginine was not seriously diminished, suggesting that at least one amino group of the lysine was free, and that most of the arginine amino groups were involved in peptide linkage. Enzyme experiments were also carried out. It was concluded ". . . dass im Glutokyrin ein Gemisch niedriger basischer Peptide vorliegt, die in bezug auf das gegenseitige Verhältnis der Basen, der Monoaminosäuren und der Iminosäuren und auch hinsichtlich ihres allgemeinen Aufbauplanes weitgehend untereinander übereinstimmen, während vermutlich die einzelnen Monoaminosäuren und Iminosäuren sich scheinbar unregelmässig innerhalb der einzelnen Peptide vertreten können."

Grassmann and Riederle (106) emphasized the importance of *yield* in peptide isolations. By applying the silver–baryta precipitation to 30 g. of "glutokyrine sulfate" they obtained: (*1*) in the precipitate, 4.2 g. of material giving on acid hydrolysis arginine as the only base; (*2*) in the filtrate, 6 g. of material giving only lysine.

Fraction 1 appeared to be a dipeptide of arginine with a monoamino acid (not glycine or glutamic acid). Determinations of amino nitrogen showed little proline and hydroxyproline could be present.

From base content, and from determinations of amino nitrogen on the original material and its basic and monoamino fractions after hydrolysis, it was concluded that fraction 2 was a tripeptide of lysine, glycine, and proline. Since it had two free amino groups, a terminal prolyl residue was excluded. A glycerol extract of kidney split one peptide bond, liberating a carboxyl but no amino group; therefore this bond involved the proline imino group. Free lysine was simultaneously produced, and the resulting dipeptide, prolylglycine, yielded one amino group on acid hydrolysis. From 125 g. of gelatin there was obtained 6 g. of this tripeptide, which thus represents a very appreciable fraction of the total

lysine of gelatin and, as well as being entirely consistent with the isolation of glycine proline anhydride from partial hydrolysates of gelatin referred to in the next section, justifies the drawing of conclusions as to the structure of gelatin.

D. NON-BASIC PARTIAL HYDROLYSIS PRODUCTS OF OTHER PROTEINS

1. Keratins

Abderhalden and Suzuki (36) investigated the products of treating goose feathers with 70 per cent sulfuric acid for 5 days at room temperature. After exact removal of the sulfuric acid with baryta, the aqueous solution was evaporated to dryness and exhaustively extracted with boiling methyl alcohol. This extract gave products in unspecified yield which were insoluble in water and in other organic solvents. Apart from the biuret reaction they did not give the usual protein color reactions, and gave on complete hydrolysis with acid only glycine and *l*-proline. Two grams of one fraction of this material on hydrolysis gave 0.39 g. of glycine and 1.75 g. of proline. The whole preparation was repeated twice with similar results. An attempt to allocate a terminal amino or imino group by naphthalenesulfonylation was unsuccessful.

Abderhalden (9) later isolated a crystalline product from the same fraction. In addition to glycine and proline it gave hydroxyproline and was considered to be an anhydride formed from 2 molecules of proline, 1 molecule of hydroxyproline, and 1 molecule of glycine by elimination of 4 molecules of water.

Abderhalden and Komm (20) investigated the products obtained by the partial acid hydrolysis of pig bristles. No yields of the products isolated were stated, and, although the stated amino acids were identified after complete hydrolysis in each case, no experimental details of the identifications were recorded. Dilute acid hydrolysis in the autoclave yielded: (*1*) glycine *l*-alanine anhydride; (*2*) a diketopiperazine consisting of leucine and proline, which had a considerably lower rotation than the synthetic product of Fischer and Reif (86); (*3*) *l*-proline *l*-valine anhydride; (*4*) a complex product containing leucine, glutamic acid, glycine, and proline; (*5*) a product consisting of proline, leucine, and alanine, which had no free amino nitrogen, but which gave one-third of its nitrogen as amino nitrogen after standing for a short while in *N* sodium hydroxide. The authors speculate at length as to the possible structure of this compound.

An idea of the yields of the above substances is given by the remark: "Immerhin hatten wir in jedem Falle Mühe für die einzelnen Bestimmungen und die totale Hydrolyse genügend Material zusammenzubekommen." The starting material was 400 g. of bristles. Hydrolysis of the bristles with 70 per cent sulfuric acid at room temperature and at 37°C. led to different products: (*1*) a crystalline optically active compound having one-half of its nitrogen as amino nitrogen and yielding leucine and serine on hydrolysis; (*2*) an amorphous fraction having one-third of its nitrogen as amino nitrogen and yielding cystine, leucine, valine, glycine, and proline on hydrolysis; (*3*) a crystalline substance giving only valine on acid hydrolysis; (*4*) further amorphous material containing cystine, leucine, valine, and glycine.

Abderhalden and Komm '(21) by dilute acid hydrolysis of pig bristles obtained in unstated yield equally inadequately characterized products as follows: (*1*) a crystalline compound yielding on hydrolysis 2 molecules of hydroxyproline and 1 molecule of glycine; (*2*) a crystalline compound thought to be leucine isoleucine anhydride; (*3*) a compound having the elementary composition of glycine alanine anhydride; its melting point was lower than that of authentic glycine *l*-alanine anhydride. "Es war nicht genügend Substanz zur weiteren Untersuchung vorhanden."

The same authors (26) obtained: (*1*) from dog hair subjected to dilute acid hydrolysis in the autoclave an unspecified yield of a crystalline product corresponding in elementary composition to alanine glycine anhydride: (*2*) from pig bristles treated in the same way: (*a*) alanine leucine anhydride (0.1 per cent yield of crude product). This had a much lower rotation than that of the synthetic material (*cf.* Fischer and Abderhalden (83)); (*b*) an unspecified yield of a further product giving alanine and leucine on acid hydrolysis, and having a lower melting point; (*c*) an unspecified yield of a crystalline product giving alanine and phenylalanine on hydrolysis. The oxidation of "keratinpepton" from sheep's wool by zinc permanganate was also studied (*cf.* the section on silk fibroin above).

2. Gelatin

The only adequately characterized non-basic partial hydrolysis product of gelatin that has been described is the anhydride of glycine and proline. This was obtained by Levene and coworkers from tryptic digests. Its subsequent isolation in good yield from acid hydrolysates (Gawrilow and Lawrowsky (96); Konuma (129)) suggests that direct linkage of glycine to proline already exists in the gelatin, and is not an artifact due to enzyme action. Grassmann and Riederle's (106) isolation of lysylprolylglycine from gelatin serves as a confirmation of this.

Levene (142) described the preparation of a crystalline product from a tryptic digest of gelatin, and gave the melting point and elementary composition of the compound and its picrate. He concluded: "Hence it is probable that the composition of the substance is $C_7H_{10}N_2O_2$, and that it is in some way related to proline." Levene and Wallace (151) gave experimental details of the preparation (for which precipitation with phosphotungstic acid was used) but reached no further conclusion as to the nature of the compound. Levene and Beatty (145, 146) investigated a preparation which had a melting point of 182–183°C., and recognized glycine and proline as its hydrolysis products. One gram gave 0.370 g. of glycine and 0.400 g. of proline. They therefore suggested that the product was glycine proline anhydride.

Fischer and Reif (86) synthesized glycine *l*-proline anhydride. Its specific rotation, $[\alpha]_D$ (water), was 216–217°, and its melting point was 203–213°C. "Im übrigen ist die Aehnlichkeit, soweit sich nach den kurzen Angaben von Levene und Beatty beurtheilen lässt, recht gross."

Levene (143) returned to the question and gave more adequate experimental

details. On tryptic digestion of gelatin for 8 months, he obtained 5–6 g. of the product from 1 kg. of gelatin. The new preparation had a melting point of 178–180°C. and a specific rotation, $[\alpha]_D$ (water), of −55°. Extraction of this product with alcohol–ether yielded material of lower melting point (168–170°C.) and rotation (−5.7°). By using a shorter period of digestion (24 days) a product with higher melting point (212°C.) and rotation (−169°) was obtained. Levene concluded that the prolonged action of the alkaline digestion medium induced racemization.

Gawrilow and Lawrowsky (96) subjected gelatin to hydrolysis by dilute sulfuric acid at 180°C. The neutralized hydrolysate was extracted with ethyl acetate. In the extract (90 g. from 500 g. of gelatin) was obtained 50 g. of crystalline material, and recrystallization of this from isoamyl alcohol–ether gave a product having a melting point of 188°C. and $[\alpha]_D$ (water) of −9.2°. Acid hydrolysis of this yielded proline and glycine, and the material was considered to be racemized glycine proline anhydride, referred to at length above. A small quantity of crystalline material having a melting point of 195–199°C. was obtained from the mother liquors. This was thought to be glycine leucine anhydride, though its melting point was lower than that of the authentic material (*cf.* Fischer and Abderhalden (82)) and the products of its hydrolysis were not satisfactorily identified (*cf.* also Ssadikow (219)).

Konuma (129) made a study of the kinetics of partial hydrolysis of gelatin, obtaining results similar to those of Uchino (225) with silk fibroin (*vide supra*). By heating gelatin with 0.15 N hydrochloric acid at 170°C., Konuma isolated a 1.43 per cent yield of glycine proline anhydride having a melting point of 207°C. and a specific rotation, $[\alpha]_D$ (water), of −185.4°. A similar yield of the same compound (racemized) was obtained from a partial hydrolysate of gelatin by alkali.

Fodor *et al.* (90, 91, 92, 94) have subjected gelatin and its enzymic hydrolysis products to the action of boiling acetic anhydride and of glycerol at high temperatures. They claim to have isolated compounds of proline and hydroxyproline with glycine and alanine, and have studied the enzymic digestion of these products. Their views as to the structure of the products in question are supported mainly by elementary analyses and by molecular-weight determinations, to which latter, as pointed out above, little significance can be attached. No adequate characterization of the amino acids resulting from hydrolysis of these products was carried out. More interest would attach to the assertion that they contain only the monoamino acids stated if it had been demonstrated that basic amino acids etc. were absent from them.

3. Elastin

Fischer and Abderhalden (82) hydrolyzed elastin with 70 per cent sulfuric acid at room temperature and at 37°C., and obtained by the esterification procedure a yield of more than 5 per cent of crude glycine *l*-leucine anhydride. This was purified by recrystallization and formally identified with the synthetic product.

The same authors (83) reported further work on a partial hydrolysate of elastin prepared in the same way. After a precipitation with phosphotungstic acid, there was found in the filtrate from this a 0.34 per cent yield of *l*-alanyl-*l*-leucine, from which alanine and leucine were identified after hydrolysis. The material was identified with synthetic *l*-alanyl-*l*-leucine.

A hydrolysate of elastin made with concentrated hydrochloric acid at 36°C. was also investigated by the esterification method, and in addition to the previously isolated glycine *l*-leucine anhydride, a small yield of partly racemized *l*-alanine *l*-leucine anhydride was obtained. This was formally identified with synthetic material, and was shown to yield alanine and leucine on hydrolysis. From the amorphous anhydride material in the mother liquors there was obtained: (*1*) An amorphous preparation giving alanine and proline on acid hydrolysis, which was thought to be alanine proline anhydride. *dl*-Alanine *dl*-proline anhydride had already been synthesized (Fischer and Suzuki (88)), and had proved to be crystalline. (*2*) An amorphous preparation which could be crystallized only by sublimation. This appeared to be glycine valine anhydride, glycine being definitely, and valine probably, identified as its hydrolysis products. Synthetic glycine *l*-valine anhydride was shown to exhibit the same peculiar crystallization phenomena (*cf.* Fischer and Scheibler (87)).

Abderhalden (1) reported the isolation of *l*-leucyl-*l*-alanine in unspecified yield from the mother liquors of the *l*-alanyl-*l*-leucine obtained above. It was formally identified with the synthetic product, and alanine and leucine were recognized as its hydrolysis products.

Abderhalden (2) hydrolyzed elastin with saturated baryta solution at 90°C. for 10 hr. After removal of baryta, the solution was treated with phosphotungstic acid, and the filtrate from this yielded optically inactive crystalline material (2.2 per cent yield). This gave glycine and leucine on acid hydrolysis, and a study of its asymmetric hydrolysis by yeast press-juice suggested that *dl*-leucylglycine rather than glycyl-*dl*-leucine was present. The possible occurrence of glycylleucine in the mother liquors was suggested.

4. Plant proteins

Fischer and Abderhalden (83) hydrolyzed gliadin with 70 per cent sulfuric acid at room temperature and at 37°C. The hydrolysate, after precipitation with phosphotungstic acid, yielded from the filtrate 0.9 per cent of *l*-leucyl-*l*-glutamic acid (through its silver salt). The product was identified with synthetic material, and gave leucine and glutamic acid on hydrolysis.

Osborne and Clapp (169) refluxed gliadin with 20 per cent sulfuric acid for 13 hr. After exact removal of the sulfuric acid with baryta, the hydrolysate was concentrated and allowed to crystallize. The first crystals (0.4 per cent yield) agreed in elementary composition with the monohydrate of a dipeptide of proline and phenylalanine, formed a copper salt (which was characterized crystallographically), and on hydrolysis yielded proline and phenylalanine. Fischer and Luniak (85) synthesized *l*-prolyl-*l*-phenylalanine, and showed that it was identical with the product of Osborne and Clapp.

Abderhalden (8) digested 500 g. of gliadin with pancreatin for 14 days. Extraction of the neutralized and dried residue with ethyl acetate gave crystals. "Ihre Menge reichte zu einer genauen Identifizierung nicht aus." The material, on the basis of melting point, specific rotation, and nitrogen content, was considered to be *l*-leucine *l*-proline anhydride (*cf.* Fischer and Reif (86)). In the mother liquors from this he found glycine *l*-proline anhydride contaminated with a compound of proline with an aromatic amino acid, perhaps phenylalanine. It was finally purified by crystallization from acetone, and had a melting point of 209°C. and specific rotation, $[\alpha]_D$ (water), of $-206.5°$ (*cf.* section on gelatin above), as well as the correct elementary composition. The yield was 0.6 per cent.

Abderhalden (1) hydrolyzed cottonseed globulin with 70 per cent sulfuric acid for 5 days at 20°C. By precipitation with phosphotungstic acid, followed by precipitation with mercuric sulfate, followed by fractional reprecipitation with phosphotungstic acid, he isolated from 1 kg. of protein 16.5 g. of a preparation giving tryptophan and glutamic acid on hydrolysis and 22.5 g. of a product giving tryptophan, leucine, and glutamic acid. Both preparations were amorphous. Molecular-weight determinations suggested that they were di- and tri-peptides, respectively. In the filtrate from the mercury precipitation, there was obtained by fractionation first with phosphotungstic acid and then with alcohol, an unspecified yield of an amorphous product which gave on hydrolysis roughly equimolecular amounts of glycine, leucine, and tyrosine. Molecular-weight determinations suggested that it was a tripeptide.

5. Casein and the phosphoproteins

Fischer and Abderhalden (79), in an attempt to isolate proline from enzymic protein digests, noted that in a tryptic digest of casein no free proline was demonstrable, but that the whole of the proline and phenylalanine were present in a combination of polypeptide type precipitable by phosphotungstic acid, and could be liberated from this material by acid hydrolysis together with alanine, leucine, glutamic acid, and aspartic acid. The same phenomenon was noted with edestin, hemoglobin, serum globulin, egg albumin, and fibrin. In edestin and serum globulin the glycine behaved in the same way. No attempt was made to fractionate or characterize the polypeptide material.

Hunter (119) extracted a tryptic digest of casein with butyl alcohol after various digestion periods, and obtained a fraction soluble in butyl alcohol which appeared to consist largely of proline peptides and diketopiperazines. Definite evidence was obtained of condensation of amino acids (loss of amino nitrogen) during the heating with butyl alcohol, but this peptide fraction could not all have had its origin in this secondary manner.

Muldrew (mentioned by Hunter (120)) fractionated the peptic digestion products of casein and showed that the "primary proteose" fraction was lacking in tyrosine and tryptophan. Hunter commented: "It is an obvious advantage in dealing with a highly complex combination of amino acids to be able to localise even two of them in one particular fragment of the whole."

Jones and Gersdorff (125) fractionated casein by digestion for 1 hr. with pepsin hydrochloride. There were obtained the following fractions:

Fraction A (precipitated during digestion)............... 21.9 per cent of casein
Fraction B (precipitated on bringing digest to pH 6)..... 12.7 per cent of casein
Fraction C (not precipitated)........................... 65.4 per cent of casein

Fractions A and B contained nearly all the phosphorus of the casein, while all the cystine that could be demonstrated was in fraction C. Significant differences in the amino acid contents of the three fractions were established, especially for tryptophan and lysine.

In an earlier paper the same authors (124) showed by the Sullivan method that free cystine is completely liberated at an early stage in the hydrolysis of casein by boiling acid, whereas no free cystine is formed from casein by the action of pepsin hydrochloride.

Rimington (187) analyzed the product obtained from casein by precipitation with acetic acid after dephosphorylation of the protein with dilute sodium hydroxide. He found little difference in its amino acid content from that of the original casein, if the loss of amide nitrogen was allowed for. Plimmer and Lawton (177) compared the amino acid content of this "depocasein" (representing 55 per cent of the original casein) with that of the original casein and, like Rimington, found little difference. Later, Macara and Plimmer (157) compared the "depocasein" with the "primary proteose" ("depocaseose") obtained from its mother liquor, and found no very considerable differences in the distribution of a large number of the constituent amino acids except in the case of tyrosine.

Abderhalden (8) obtained 0.6 per cent of leucine valine anhydride from a digest of casein prepared by the action of 70 per cent sulfuric acid at 18°C. This was accompanied by a trace of alanine phenylalanine anhydride. Later Abderhalden (10) obtained 0.25 per cent of the same leucine valine anhydride from a hydrolysate of casein prepared with hot dilute sulfuric acid. By extraction with methyl alcohol there was also obtained from the same hydrolysate an unspecified yield of a dipeptide which was identified as partly racemized *l*-alanyl-*l*-leucine. In the mother liquors from this was obtained 0.35 per cent of a crystalline material which gave *dl*-proline, *l*-leucine, and *l*-alanine on acid hydrolysis; this was thought to be some sort of tripeptide anhydride.

Abderhalden and Sickel (30) reported the isolation from a tryptic digest of casein[2] of 0.28 per cent of a crystalline material which gave tyrosine and proline on acid hydrolysis but which showed deviations from the expected behavior of a dipeptide. The authors recorded extensive observations on the chemical behavior of this compound, and in a subsequent paper (31) described the syn-

[2] It is of interest for the history of the discovery of the amino acids to note that Abderhalden (6) obtained from a tryptic digest of casein, by precipitation with mercuric sulfate, a sulfur-rich crystalline material which looked like leucine but which was more soluble in water. On the basis of present-day knowledge it can be deduced with certainty that this was an impure specimen of methionine.

Schmidt (197) supplemented his earlier communication (196) with an account of the isolation of an unspecified yield of phosphorus-rich material from a tryptic casein digest by lead acetate precipitation followed by precipitation of the barium salt by alcohol. The material had the atomic ratio nitrogen/phosphorus = 2, and in its hydrolysate only glutamic acid and serine could be demonstrated in addition to phosphoric acid. Barium salts with a higher nitrogen/phosphorus ratio gave in addition "ein Leucin" on hydrolysis.

Sorimati (217) studied the liberation of amino nitrogen and inorganic phosphorus from casein and its phosphopeptone under various conditions of hydrolysis, and described the preparation of 7 g. of the barium salt of the glutamic acid serine phosphoric ester dipeptide by direct acid hydrolysis of 200 g. of casein. This compound had the correct elementary composition, and one-half of its nitrogen was amino nitrogen. On acid hydrolysis it yielded serine phosphoric ester; glutamic acid was not isolated. The action of phosphatases on these various products was studied.

Herd (111) made kinetic studies of the enzymic and alkaline hydrolysis of "paranuclein" from casein; she also (112) studied similar digestion products of other phosphoproteins (as well as proteins that had been artificially phosphorylated). (*Cf.* Herd (113)).

Rapoport (185) claimed that the phosphorus/serine molecular ratio in casein was 4:3, and that other residues than serine must be involved in the linkage of organic phosphorus. He determined serine colorimetrically in the hydrolysate after deamination to glyceric acid. A 1:1 ratio of phosphorus to serine was claimed for vitellinic acid.

Similar studies of the tryptic digestion of casein were made by Grabar (102), who subsequently (103) studied a phosphorus-rich fraction obtained in the early stages of tryptic digestion. He noted that it gave a negative reaction for tryptophan and a very faint Millon reaction, and prepared its insoluble copper derivative.

Damodaran and Ramachandran (57) digested the "paranuclein" of casein with trypsin. The digest was precipitated with lead, and the precipitated material was redigested with trypsin and precipitated as its barium salt with alcohol. This led to a "phosphopeptone" of constant composition, having one-tenth of its nitrogen in the form of amino nitrogen. Amino acid analysis of this decapeptide showed that it was composed of 4 molecules of serine, 3 molecules of glutamic acid, and 3 molecules of isoleucine, and contained three phosphoric acid residues, presumably bound to the serine residues in ester linkage. Considerable decomposition of the serine during acid hydrolysis was noted, the main products being glyceric acid and ammonia. No other amino acid could be isolated from the material. After dephosphorylation by alkali, the material could be hydrolyzed by trypsin, so it is presumably to the presence of the phosphoric acid residues that it owes its trypsin-resistance.

Products of similar qualitative amino acid composition have been isolated from casein by Lowndes *et al.* (155) and by Rimington (190), who subjected his original material to a reinvestigation.

IV. Conclusions

No general picture of protein structure can be said to emerge from the studies reviewed above. The most complete structural investigation is undoubtedly that of clupein, and even for this substance Felix's proposed formula, although entirely consistent with the manifold experimental data that have accumulated, is by no means rigidly established. Any attempt to construct a formula for silk fibroin is made difficult by the questionable homogeneity of this substance. Except in the protamines, tussore silk, and vitellinic acid, few cases of direct linkage of two amino acid residues of the same species have been established; direct association of different amino acids has been proved in a number of cases, of which the following seem to be the outstanding examples: (1) glycine–alanine and glycine–tyrosine in silk fibroin; (2) glycine–leucine and alanine–leucine in elastin; (3) proline–phenylalanine and leucine–glutamic acid in gliadin; (4) lysine–proline–glycine in gelatin; and (5) valine–leucine, isoleucine–glutamic acid–serine (phosphoric ester) in casein.

The isolation of such groupings in significant yield does suggest some regularity of structure such as that put forward by Bergmann and Niemann, rather than statistically random occurrence of amino acid residues along a peptide chain. At the present stage there is little justification for further speculation.

It is clear that future progress in this field is bound up with the improvement of technique. The techniques employed for the separations described in this review have proved themselves over and over again to be inadequate. It is time that this was generally recognized, and in concluding the present review I shall deal briefly with the technical aspects of peptide separation and point out some of the probable lines of advance.

For hydrolysis, concentrated acids acting at low temperatures seem to be at present the most desirable reagents. The disadvantages of the use of alkali are well known. Hydrolysis at high temperatures favors diketopiperazine formation and probably other changes. The isolation of a diketopiperazine yields no information, such as is given by a dipeptide, as to the order of the component residues in the peptide chain.

The work of Levene and Abderhalden and their respective collaborators has made it clear that different peptide bonds show very different stabilities towards acid and alkaline hydrolysis. One may tentatively picture that the course of hydrolysis of a protein involves first the preferential splitting of certain bonds; immediately this has occurred the effect of the liberated $-NH_4^+$ and $-COO^-$ will come into action: the bond adjacent to a free α-amino group is likely to acquire increased resistance to hydrolysis by acids (cf. Moggridge and Neuberger (163) and Neuberger and Pitt Rivers (167) on the acid hydrolysis of the N-acetyl-methylglucosaminides). Converse effects may be expected with alkali, and it is possible that charged groups in the side chains of amino acid residues may play a similar rôle to those of the main chain in determining hydrolysis. On this view it would be expected that dipeptides would have a special resistance to hydrolysis, and there appears to be some experimental evidence in favor of

this. It is clear that the passage from the intact protein to its ultimate hydrolysis products may take a number of different paths. Very little is known as to the extent to which the path taken may be altered by varying the conditions of hydrolysis. Nevertheless, hydrolysis by acid or alkali, however carefully controlled, does not seem likely to show the same selectivity in the splitting of peptide bonds as enzymes are known to possess, and it is to be hoped that the more accurate determination of the specificity of proteolytic enzymes in hydrolysis and synthesis will soon permit their unequivocal use in the interpretation of protein structure.

Non-isolative studies of partial hydrolysates and partial hydrolysis products have proved of value. The Van Slyke determination of amino nitrogen (in spite of its anomalous results with such compounds as glycylglycine (Van Slyke (226)) and glutathione (cf. Hopkins (117)) has certainly not been used to full effect in the studies reviewed above. The ninhydrin–carbon dioxide reaction of Van Slyke and Dillon (227) (cf. Christensen, West, and Dimick (49)) promises to prove of value in detecting free amino acids; there is also available the Sullivan reaction in the special case of cystine. It seems probable also that hydroxyamino acids such as serine and threonine may be estimated by their reaction with periodic acid (cf. Nicolet and Shinn (168) and Martin and Synge (159)) when both the OH and NH_2 groups of the residue are free.

Where the methods employed in the past for the separation of recognizable partial hydrolysis products of proteins have not been purely empirical (e.g., direct crystallization, precipitation with organic solvents), they have usually depended on a crude analogy between the behavior of the free amino acids and of peptides containing these residues (e.g., precipitation with phosphotungstic, picric, picrolonic, or flavianic acid or with the salts of metals such as mercury, copper, iron, uranium, barium, silver, lead, etc.). In this connection it is odd that cuprous oxide, which is a selective precipitant for compounds containing a potential thiol group (Hopkins (117); cf. Pirie (175)), has not so far been employed in this field.

It is likely that in the future solid-phase separations, which are by their nature slow and unreliable (especially when the compounds concerned do not readily crystallize), will give way to methods based on diffusion, adsorption (cf. Felix and Lang (73), who tested the use of permutit in the separation of the peptic hydrolysis products of gelatin), electrophoresis (cf. Albanese (37)), liquid extraction, distillation, etc. To such methods, whether based on kinetic or equilibrium properties, counter-current technique can be applied, and the most delicate separations effected. Liquid extraction has been used (e.g., by Ssadikow) for isolating diketopiperazines from partial protein hydrolysates, and Hunter (119) employed Dakin's butyl extraction method on a partial hydrolysate of casein. Chemical substitution of the partial hydrolysis products, and the application of counter-current methods (cf. Martin and Synge (158)) may extend the applicability of liquid–liquid extraction. Abderhalden and Kröner (27) were unsuccessful in distilling the esters of benzoylpeptides, but Gurin (108) had more success with the ethyl and butyl esters of N-benzenesulfonyl peptides,

and he gives references to the previous literature on volatile derivatives of amino acids. Molecular distillation will prove a more satisfactory purification technique when counter-current principles have been applied to it. Methods depending on specific chemical reactions, such as Fischer and Abderhalden's condensation of dipeptide ethyl esters to diketopiperazines, are likely also to find employment.

When isolation, structural characterization, and synthesis of a partial hydrolysis product have been carried through, the 'isotope dilution' method of Rittenberg and Foster (192) is likely, as already pointed out, to prove of great value in its quantitative determination in the partial hydrolysate.

A number of methods have been used for the elucidation of the order of the amino acid residues in simple peptides. Fischer employed naphthalenesulfonylation followed by acid hydrolysis, which yields the amino acid having a free NH_2 group in the form of its acid-resistant naphthalenesulfonyl derivative. Poor yields are often encountered in the naphthalenesulfonylation. Benzoylation has been employed in the same way, although Abderhalden and Bahn have shown that some benzamino acids, e.g., benzoylserine, are fairly readily hydrolyzed by acid. Methylation and condensation with dinitrophenyl chloride have also been employed for the allocation of free amino groups.

Schlack and Kumpf (195) worked out a stepwise degradation procedure in which the amino acid residue bearing the carboxyl group of the peptide is removed as its thiohydantoin by successive treatment with ammonium isothiocyanate in acetic anhydride and with alkali.

Bergmann, Kann, and Miekeley (40) allocated the free amino group by condensation with phenyl isocyanate. Subsequent acid hydrolysis gives this terminal amino acid residue as its phenylhydantoin. Abderhalden and Brockman (16) elaborated this method to deal also with the free carboxyl group by condensation with benzylamine. Goldschmidt and Wiberg (100) have employed hypobromite to obtain the amino acid with free amino group as the next lower nitrile of the homologous series.

Bergmann and Zervas (45) have worked out a method of stepwise degradation of benzoyl peptides through the carbobenzoxy derivative of the azide, which removes the residue carrying the free carboxyl group as the next lower aldehyde in the homologous series, and leaves the rest of the peptide in the form of its amide.

Nitrous acid may be employed for selective deamination of the residue carrying the free amino group. Racemization with alkali or, as suggested by Cahill and Burton (48), with ketene may also prove useful for structural elucidation, and serological methods are likely in the future to be a valuable aid.

To conclude, it seems that the main obstacle to progress in the study of protein structure by the methods of organic chemistry is inadequacy of technique rather than any theoretical difficulty. It is likely that the development of new methods of work in this field will lead us to a very much clearer understanding of the proteins.

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THE CHEMISTRY OF PHENOXATHIIN AND ITS DERIVATIVES

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CONTENTS

I. INTRODUCTION

A search of the literature reveals that no general survey of the chemistry of phenoxathiin and its derivatives has ever been published. It is believed that the increasing interest in this compound and its recent commercial availability warrant a review at the present time.

II. NOMENCLATURE

Several names have been applied to the parent heterocyclic compound. Phenoxathiin is given as the preferred name by Patterson and Capell (25), and will be used in this paper. Other names often encountered in the literature are phenoxthin, phenothioxin, dibenzothioxin, and dibenzo-1,4-oxthiin.[1]

No generally accepted method of numbering exists, so that care must be taken to observe the notation used in any particular paper. The numbering given as preferred by Patterson and Capell (25) and used here is indicated in the following formula:
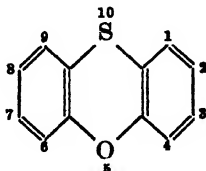
[1] The numbering used in this name is not compatible with the preferred numbering of Patterson and Capell

More frequently encountered is the numbering originally proposed by Mauthner (21):
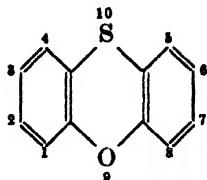
Also in use is the numbering proposed by Pollak, Riesz, and Riesz (28):
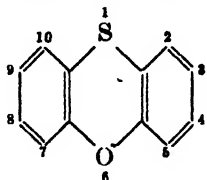
III. Phenoxathiin and its Oxides

Phenoxathiin is a white crystalline compound, the pale yellow color sometimes observed (7) probably being due to impurities. Three methods of preparation of phenoxathiin have been used. Most widely encountered is the reaction between diphenyl ether and sulfur in the presence of anhydrous aluminum chloride (1, 2, 9, 11, 38, 39, 40):
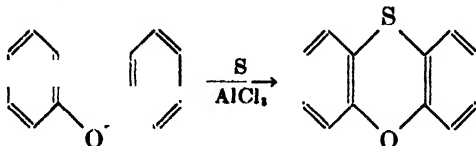
This has been called the Ferrario reaction. Greater than 80 per cent yields of purified product have been obtained in this way (39).

When phenoxatellurin is heated with sulfur, phenoxathiin is formed in over 90 per cent yield (7):
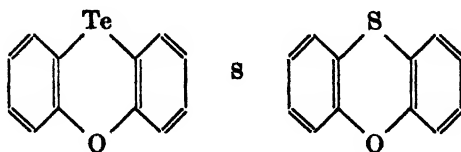
A third method is decarboxylation of phenoxathiin-3-carboxylic acid by heating with calcium oxide (22):
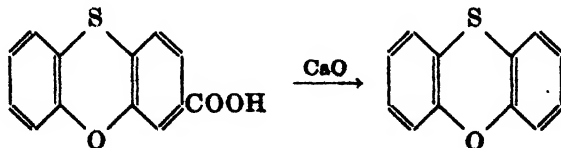
Hinsberg (17) in 1929 reported the preparation of an isophenoxathiin-10-dioxide in 0.5 per cent yield by the action of 70 per cent perchloric acid on commercial phenyl sulfide or by the action of hydrogen peroxide on "isophenyl sulfide." The substance has 0.5 molecule of water of crystallization and melts at 225°C. Phenoxathiin-10-dioxide melts at 147–148°C. The isomerism is explained on the basis of two centers of valency for the sulfur atom. This explanation does not agree with present theory and the experimental work seems questionable.

The melting point of phenoxathiin is variously given as from 56° to 61°C. (2, 7, 22, 39, 40); Suter, McKenzie, and Maxwell (40) report the melting point of a sample, recrystallized until pure when examined with a polarizing microscope, as 57.5–58°C. Phenoxathiin boils at 311°C. at 745 mm. pressure, with slight decomposition (38); at 23 mm. the boiling point is 185–187°C. (40), and at 15 mm. it is 180–183°C. (39). Phenoxathiin is, therefore, only difficultly volatile with steam (22). It is readily soluble in all the usual organic solvents.

Wood, McCale, and Williams (44) report that x-ray measurements show that the crystal lattice is Γ_0 and the space group $P2_12_12_1(D_2^4)$. This is enantiomorphic, and the crystals are not holohedral as indicated by external symmetry measurements.

Drew (6) discusses a formulation of the electronic structure of phenoxathiin.

The reactions of phenoxathiin are given for the most part in the section on phenoxathiin derivatives in Part IV, but a few not included there will be mentioned here.

Ferrario (9) states that phenoxathiin can be converted to dibenzofuran by heating with metallic copper at 250°C.:
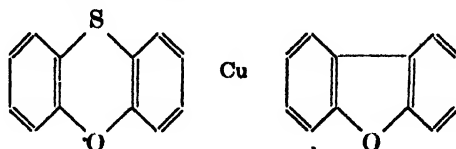
However, Gilman, Van Ess, Willis, and Stuckwisch (11) and Suter, McKenzie, and Maxwell (40) could not duplicate his results.

When treated with oxidizing agents, phenoxathiin can form either the 10-oxide or the 10-dioxide:
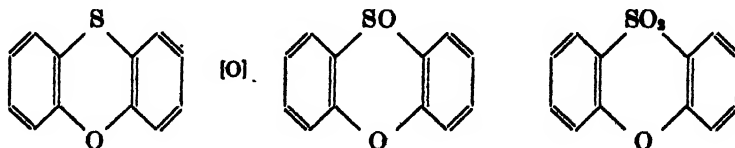
With a mixture of concentrated nitric and acetic acids, the 10-oxide is formed in 93 per cent yield (43). The oxide is also obtained by the action of hydrogen peroxide on an acetic acid solution of phenoxathiin. When phenoxathiin is dissolved in cold concentrated sulfuric acid and allowed to stand for 3 hr., one-half of it is converted into the oxide (7).

Phenoxathiin-10-oxide forms colorless crystals, m.p. 158–159°C., when crystallized from acetic acid or from benzene. It is rather sparingly soluble in hot water and does not form an hydroxide (7).

When it is heated with zinc dust and acetic acid, phenoxathiin-10-oxide is reduced to phenoxathiin. This reduction also takes place when it is heated with acetic and hydrochloric acids, the chlorine evolved partly chlorinating the resulting phenoxathiin.

If phenoxathiin-10-oxide is treated with cold concentrated sulfuric acid for 2 hr., a 35 per cent yield of phenoxathiin and larger amounts of a brown amorphous substance are obtained. This compound is considered to have the following structure:
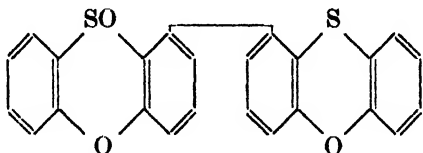
With a 30-min. treatment with concentrated sulfuric acid on the water bath, a 29 per cent yield of phenoxathiin is formed; and if the time is limited to 5 min., both phenoxathiin and unchanged 10-oxide are recovered (7). In the two latter cases the brown amorphous substance is also obtained.

Phenoxathiin-10-dioxide is formed when phenoxathiin is oxidized by chromic acid (22, 43), by potassium permanganate, or by prolonged treatment with hydrogen peroxide (7). It is obtained as colorless needles, m.p. 147–148°C., after recrystallization from dilute acetic acid.

Phenoxathiin gives a violet color when dissolved in cold concentrated sulfuric acid. The 10-oxide also forms a violet solution, which turns blue irreversibly on warming; the 10-dioxide does not give a color. The violet color has been attributed by Drew (7) to the formation of thionylium compounds of the following type:

$$SO_4H^-$$
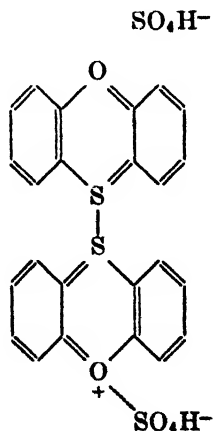
Hilditch and Smiles (15, 16) postulated an explanation on the basis of the formation of thionium salts, such as:
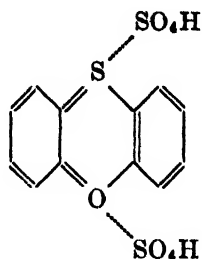
Moir (24) examined a series of sulfuric acid solutions of compounds in which two benzene rings are connected, in o-positions, by two identical or different elements, including phenoxathiin, its oxide, and dioxide. He found that the wave numbers of the strongest lines of most of the substances examined can, by certain divisions, be made to yield the same quotient.

IV. Derivatives of Phenoxathiin and its Oxides

A. DERIVATIVES WITH ONE TYPE OF FUNCTIONAL GROUP

1. Alkyl derivatives

Three monomethylphenoxathiins have been prepared according to the Ferrario reaction by condensation of the three tolyl phenyl ethers with sulfur in the presence of aluminum chloride (38). o-Tolyl phenyl ether yields the 4-methyl derivative, and the para compound yields the 2-methyl derivative. With m-tolyl phenyl ether either 1- or 3-methylphenoxathiin may be formed. Suter and Green assume that the 3-methyl compound is the more probable.

The corresponding 10-dioxides are prepared by oxidation of the phenoxathiins with hydrogen peroxide. Data of Suter and Green are given in table 1.

One dimethyl derivative, 2,8-dimethylphenoxathiin, has been prepared. Hilditch and Smiles (15, 16) obtained it by treatment of 3,3'-dimethyl-6,6'-dihydroxydiphenyl sulfoxide with cold sulfuric acid for several hours:
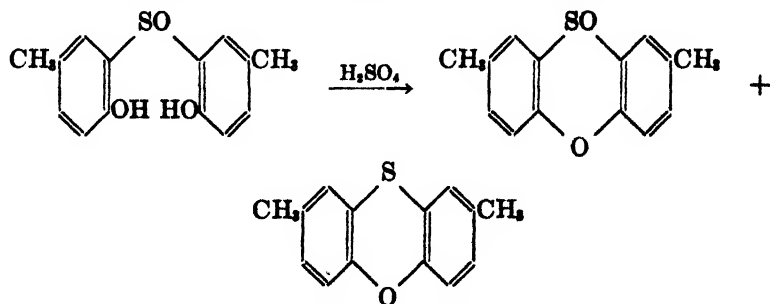
A mixture of 2,8-dimethylphenoxathiin and the 10-oxide is formed. The reaction is not a simple dehydration, but probably involves the formation of a sul-

fonium quinone and a phenothioxonium hydroxide by intramolecular rearrangements, followed by loss of water:
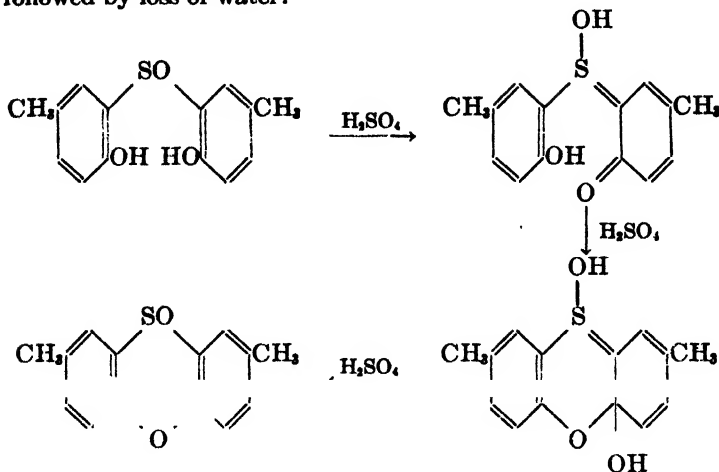
If the treatment with sulfuric acid is for 7 or 8 min. only, 2,8-dimethylphenothioxonium hydroxide can be isolated as orange leaflets, m.p. 105–110°C. This substance forms a buff-colored platinichloride and a greenish brown picrate. Reduction with zinc dust and acetic acid yields 2,8-dimethylphenoxathiin. With aqueous alkali, 2,8-dimethylphenoxathiin is also formed, together with other unidentified compounds (16).

Tomita (42) obtained 2,8-dimethylphenoxathiin, m.p. 73–74°C., from di-*p*-tolyl ether by the Ferrario reaction:
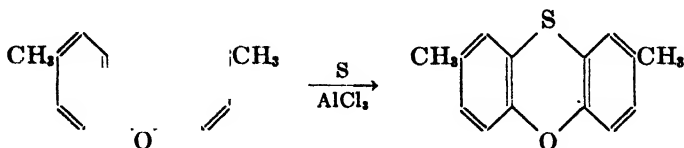
Oxidation of 2,8-dimethylphenoxathiin gives a variety of products. With cold hydrogen peroxide, 2,8-dimethylphenoxathiin-10-oxide, m.p. 132–133°C., is produced. The oxide can be reduced to the original compound with zinc dust and glacial acetic acid. When a solution of the oxide in cold acetic acid is treated with the calculated quantity of potassium permanganate, the 10-dioxide is formed as colorless prisms, m.p. 172°C. (15). Tomita (42) reported that 2,8-dimethylphenoxathiin can be oxidized to give phenoxathiin-10-dioxide-2,8-dicarboxylic acid. The methyl ester melts at 204–208°C.

2,8-Diethylphenoxathiin was prepared by reduction of 2,8-diacetylphenoxathiin or of 2,8-di-(β-chloroacetyl)phenoxathiin with zinc amalgam (42). On oxidation, 2,8-diethylphenoxathiin-10-dioxide is formed.

Smith and Moll (31, 32, 35) state that alkyl groups may be introduced by treating phenoxathiin or halophenoxathiins with an alcohol or an olefin in the presence of an acid-activated bleaching earth as a catalyst. Cycloalkyl groups

are introduced by treating phenoxathiin, or a halogen-, alkyl-, or phenyl-substituted phenoxathiin, with a cycloalkylating agent. When cycloalkyl or substituted cycloalkyl halides are employed as cycloalkylating agents, aluminum bromide or aluminum chloride is suitable as a catalyst. With cycloalkenes or hydroxycycloalkanes, an acid-activated bleaching earth serves as a catalyst. Phenoxathiins substituted with a cycloalkyl group may be oxidized to the corresponding 10-oxides and 10-dioxides with nitric acid (34).

TABLE 1

Methylphenoxathiins

COMPOUND	MELTING POINT	PERCENTAGE YIELD	MELTING POINT OF 10-DIOXIDE
	°C.		°C.
2-Methylphenoxathiin...	38–39	49	134–135
3(?)-Methylphenoxathiin	83–84	77	138–139
4-Methylphenoxathiin.................	b.p. 186–187 (14 mm.)	46	141–142

2. Halogen derivatives

Only chloro and bromo derivatives of phenoxathiin have been prepared.

Direct chlorination of phenoxathiin was studied by Suter and Green (38). A compound was isolated from the monochlorinated fraction, b.p. 212°C. at 28 mm., which was not thought to be identical with any of the three monochloro compounds prepared by the Ferrario reaction. It was therefore assumed to be 1-chlorophenoxathiin. Substitution in the 1-position on chlorination is unexpected, since bromination is known to give 2-bromophenoxathiin (40). The compound melts at 81–82°C., and forms a 10-dioxide, m.p. 178–179°C., on oxidation with hydrogen peroxide.

2-Chlorophenoxathiin, m.p. 88–89°C., was prepared in 65 per cent yield by the Ferrario reaction by heating *p*-chlorophenyl phenyl ether with sulfur and aluminum chloride (1, 38). Kent and Smiles (19) obtained the corresponding 10-dioxide by the action of aqueous alkali on 5-chloro-2-hydroxy-2'-nitrodiphenyl sulfone. 4-Chloro-2-sulfino-2'-nitrodiphenyl ether, the primary product, loses nitrous acid and forms 2-chlorophenoxathiin-10-dioxide:
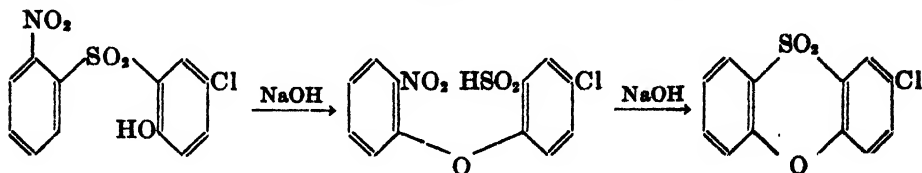
This reaction was noted as a side reaction in a study of the rearrangement of *o*-hydroxysulfones to *o*-sulfinodiphenyl ethers in alkaline solution and was not studied extensively. Suter and Green (38) prepared the 10-dioxide, m.p. 158–159°C., by oxidation of 2-chlorophenoxathiin with hydrogen peroxide.

By heating *m*-chlorophenyl phenyl ether with sulfur and aluminum chloride, Suter and Green (38) obtained a monochlorophenoxathiin, m.p. 59–60°C., in 71

per cent yield.   This was assumed to be 3-chlorophenoxathiin, although it could also be the 1-chloro compound.   The corresponding 10-dioxide, m.p. 152–153°C., was prepared by oxidation with hydrogen peroxide.

4-Chlorophenoxathiin was prepared from o-chlorophenyl phenyl ether in 50 per cent yield by the Ferrario reaction (38).   It is an oil, b.p. 192–193°C. at 7 mm.   On oxidation with hydrogen peroxide, it is converted into the 10-dioxide, m.p. 148–149°C.   Gilman, Van Ess, Willis, and Stuckwisch (11) showed that phenoxathiin undergoes metalation with n-butyllithium in the 4-position by conversion of the organometallic compound so formed into 4-chlorophenoxathiin-10-dioxide according to the following scheme:
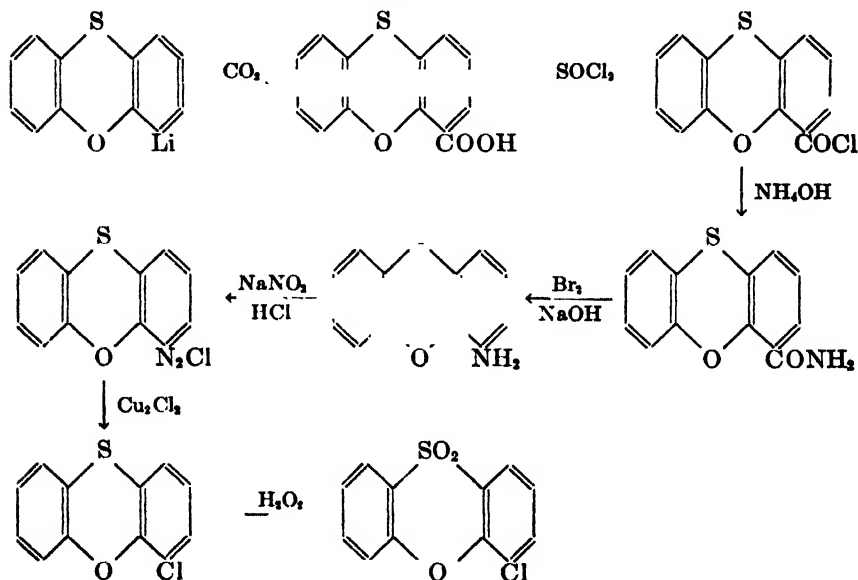
One dichlorophenoxathiin has been prepared.   Its 10-oxide was obtained in 25 per cent yield by treating "p-chlorophenol-o-sulfoxide" with cold concentrated sulfuric acid.   Recrystallization from ethyl alcohol gave shiny crystals, m.p. 168°C.
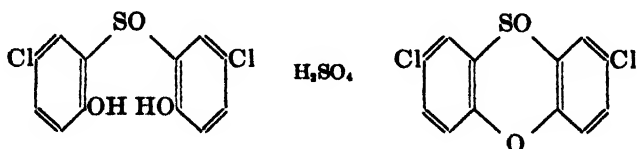
Hilditch and Smiles (15) regard the compound as being probably 2,8-dichlorophenoxathiin-10-oxide, as shown in the equation, although the structure of the "p-chlorophenol-o-sulfoxide" is not definitely established.   If the treatment with sulfuric acid is limited to 15 min., an unstable compound, probably 2,8-dichlorophenothioxonium hydroxide, is formed as pale orange plates, m.p. 142–145°C. (16).   On treatment of the oxide or the thioxonium hydroxide with

zinc dust and glacial acetic acid, or of the thioxonium hydroxide with cold aqueous alkali, 2,8-dichlorophenoxathiin, m.p. 135°C., is obtained. 2,8-Dichlorophenoxathiin-10-dioxide, m.p. 196°C., is prepared by oxidation of the monoxide with cold potassium permanganate solution. Suter, McKenzie, and Maxwell (40) obtained the same dichlorophenoxathiin by heating with phosphorus pentachloride the dichloride of the disulfonic acid obtained by sulfonation of phenoxathiin with chlorosulfonic acid.

Drew (7) reports that, in the reduction of phenoxathiin-10-oxide with acetic and hydrochloric acids, the resulting phenoxathiin is partly chlorinated by the chlorine which is evolved.

Pützer and Muth (29) state that halogen derivatives of phenoxathiin can be converted to the corresponding hydroxy derivatives by heating them with aqueous caustic alkalies or alkaline earths under pressure.

The only monobrominated phenoxathiin of definitely known structure is the 2-bromo compound. This was obtained in yields of over 80 per cent as crystals, m.p. 59–60°C., by treatment of phenoxathiin with an equimolar quantity of bromine (11, 40). It is difficult to form a Grignard reagent of 2-bromophenoxathiin directly (40).

The Ferrario reaction cannot be used in the preparation of bromo compounds, as only tars are obtained (1, 38, 40).

The only known dibromo compound is the 2,8-dibromo derivative. This was first prepared as crystals, m.p. 92°C., by heating the sodium derivative of 2,5,5'-tribromo-2'-hydroxydiphenyl sulfide with copper sulfate (37):
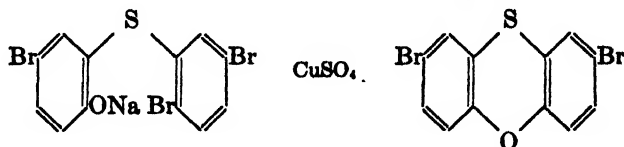
It was also obtained by Suter, McKenzie, and Maxwell (40) in 75 per cent yield by bromination of phenoxathiin with a slight excess of bromine. Oxidation with hydrogen peroxide gave 2,8-dibromophenoxathiin-10-dioxide, m.p. 185–186°C., in 92 per cent yield. They established the positions at which the bromine entered by determining that the 10-dioxide of the dibromocompound so prepared was identical with the compound synthesized in the following way:
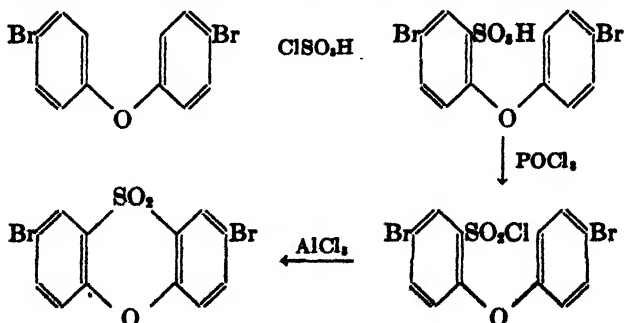
3. Nitro derivatives

2-Nitrophenoxathiin is the only mononitro derivative known. A mixture of this compound, m.p. 140°C., and its 10-oxide was obtained by treating 4-nitro-2-sulfinodiphenyl ether with acetic anhydride and concentrated sulfuric acid (20):
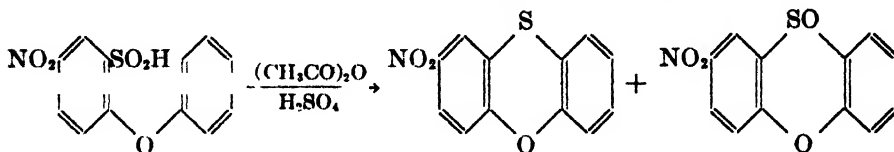
On heating with nitric acid, 3-nitrophenoxathiin is converted to the 10-dioxide, m.p. 205-206°C.

The first compound containing the phenoxathiin nucleus to be prepared was the dinitro derivative of Mauthner (21). It was obtained by reduction with sodium amalgam of the monosodium salt of *o,o'*-dihydroxydiphenyl disulfide to the disodium salt of 2-mercaptophenol, which was condensed with picryl chloride in the presence of sodium hydroxide. Orange-red leaflets, m.p. 187°C., were formed in 80 per cent yield. Mauthner represented the reaction by the following equation:
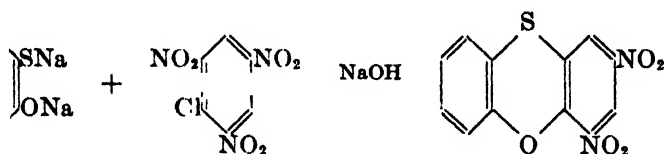
Stevenson and Smiles (37), however, in studying the reaction between 2-hydroxy-1-naphthyl mercaptan and picryl chloride, observed that the dinitro compound so obtained was identical with that formed by the action of alkali on the *S*-picryl derivative of 2-acetoxy-1-naphthyl mercaptan:
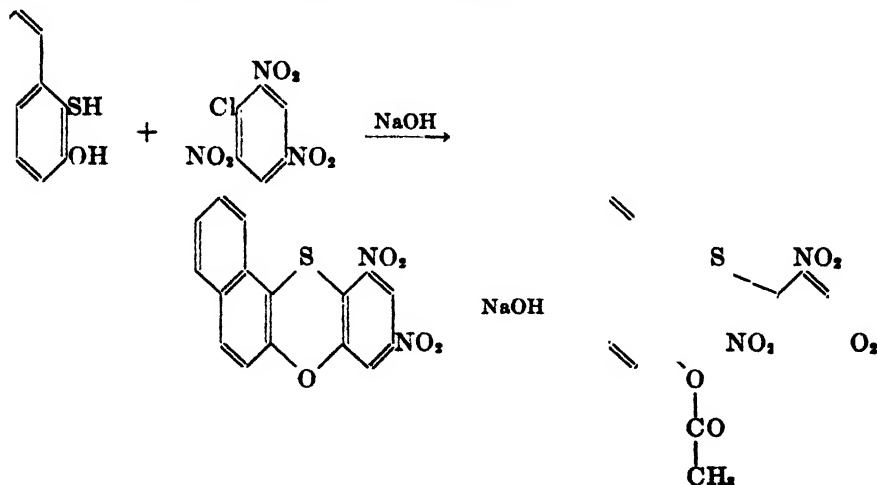
This would indicate that the elimination of nitrous acid involves the hydroxyl and not the thiol group. Mauthner's dinitro compound would therefore be the 1,3-dinitro compound:
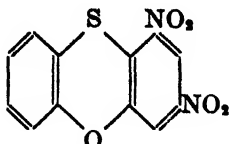
Oxidation of the dinitrophenoxathiin with nitric acid gives a 73 per cent yield of the 10-oxide, yellow needles melting at 202–203°C. With chromic acid, the 10-dioxide is formed as light yellow crystals, m.p. 256.5–257°C., in 86 per cent yield.

Nitrophenoxathiins cannot be prepared from the corresponding nitrophenoxatellurins, for they decompose explosively when heated with sulfur (7).

4. Amino derivatives

4-Aminophenoxathiin hydrochloride, m.p. 223–225°C. with decomposition, was prepared by Gilman, Van Ess, Willis, and Stuckwisch (11), as shown in section 2. It was also obtained by them in 70 per cent yield by the action of α-methylhydroxylamine on 4-phenoxathiinyllithium.

One diamino compound is known. This compound has the same orientation as Mauthner's dinitro compound, and is therefore either the 1,3- or the 2,4-dinitro derivative. It was obtained as colorless needles, m.p. 158°C., by reduction of Mauthner's dinitro compound with tin and hydrochloric acid or of the corresponding 10-oxide with zinc dust and glacial acetic acid (21). A solution of the hydrochloride changes to a color similar to Bismarck brown on the addition of nitrite. The sulfate was obtained by treating an ether–alcohol solution of the amine with dilute sulfuric acid.

The diacetyl derivative was obtained in 65 per cent yield as colorless needles, m.p. 224–225°C., by heating the diamine with acetic anhydride. With benzoyl chloride, the diamine gave the dibenzoyl derivative, m.p. 257°C., in 72 per cent yield.

When the 10-dioxide of Mauthner's dinitro compound was reduced with stannous chloride, the 10-dioxide of the diamino compound was obtained in 85 per cent yield as colorless needles, m.p. 228°C.

5. Hydroxy derivatives

Pützer and Muth (29) state that hydroxy derivatives of phenoxathiin may be prepared by treating the corresponding halogen derivatives with aqueous alkalies or alkaline earths under pressure.

6. Phenoxy derivatives

2-Phenoxyphenoxathiin can be prepared by condensing 2-bromophenoxathiin with the potassium salt of phenol in the presence of copper powder (38):
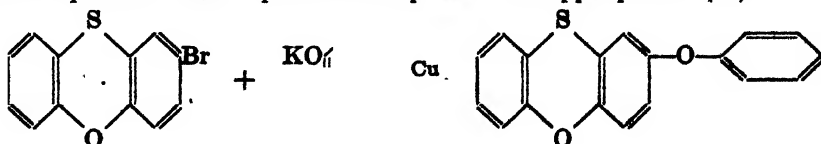
The crude product was formed in 58 per cent yield and, after recrystallization from ethyl alcohol, melted at 81–82°C.

When heated with excess hydrogen peroxide, 2-phenoxyphenoxathiin is converted into the 10-dioxide, m.p. 112–113°C. 2-Phenoxyphenoxathiin evolves hydrogen sulfide slowly when heated at 40°C. with sulfur and aluminum chloride. At higher temperatures decomposition sets in with the evolution of hydrogen chloride, but no diphenoxathiin was isolated.

o-Methoxyphenyl phenyl ether gave no evidence of undergoing the Ferrario reaction at 100°C.

7. Acetyl derivatives

2-Acetylphenoxathiin is obtained in 58 per cent yield by a Friedel–Crafts reaction between phenoxathiin and acetyl chloride (40):
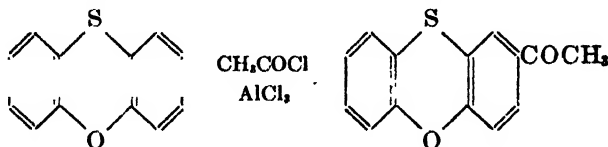
It is a light yellow powder melting at 111–112°C. The phenylhydrazone melts at 93.5–94.5°C.; the oxime melts at 142–143°C.

That the acetyl group has entered in the 2-position is shown by oxidation of the compound to the corresponding acid with bleaching powder. The phenoxathiin-2-carboxylic acid, m.p. 259–260°C., thus obtained in 60 per cent yield, is identical with the acid obtained by the action of carbon dioxide on the Grignard reagent from 2-bromophenoxathiin.

2,8-Diacetylphenoxathiin was prepared from phenoxathiin by Tomita (42). When reduced with zinc amalgam, it gave 2,8-diethylphenoxathiin. Oxidation of 2,8-diacetylphenoxathiin gave phenoxathiin-10-dioxide-2,8-dicarboxylic acid, m.p. > 300°C.

When phenoxathiin is condensed with chloroacetyl chloride using aluminum chloride, 2,8-di-(β-chloroacetyl)phenoxathiin, m.p. 193°C., is obtained (42):
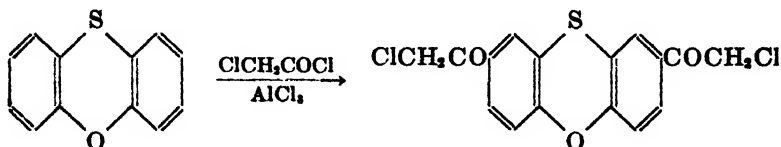
With piperidine, 2,8-di(β-chloroacetyl)phenoxathiin gives 2,8-di(β-piperidylacetyl)phenoxathiin, m.p. 105°C., which on reduction with sodium amalgam forms 2,8-di(α-hydroxypiperidylethyl)phenoxathiin, m.p. 133°C. When the reduction is carried out with zinc amalgam, 2,8-diethylphenoxathiin is formed. Oxidation of 2,8-di-(β-chloroacetyl)phenoxathiin with hydrogen peroxide gives 2,8-di(β-chloroacetyl)phenoxathiin-10-dioxide, m.p. 224–229°C. (43); further oxidation gives phenoxathiin-10-dioxide-2,8-dicarboxylic acid (42). These reactions are shown in the following equations:
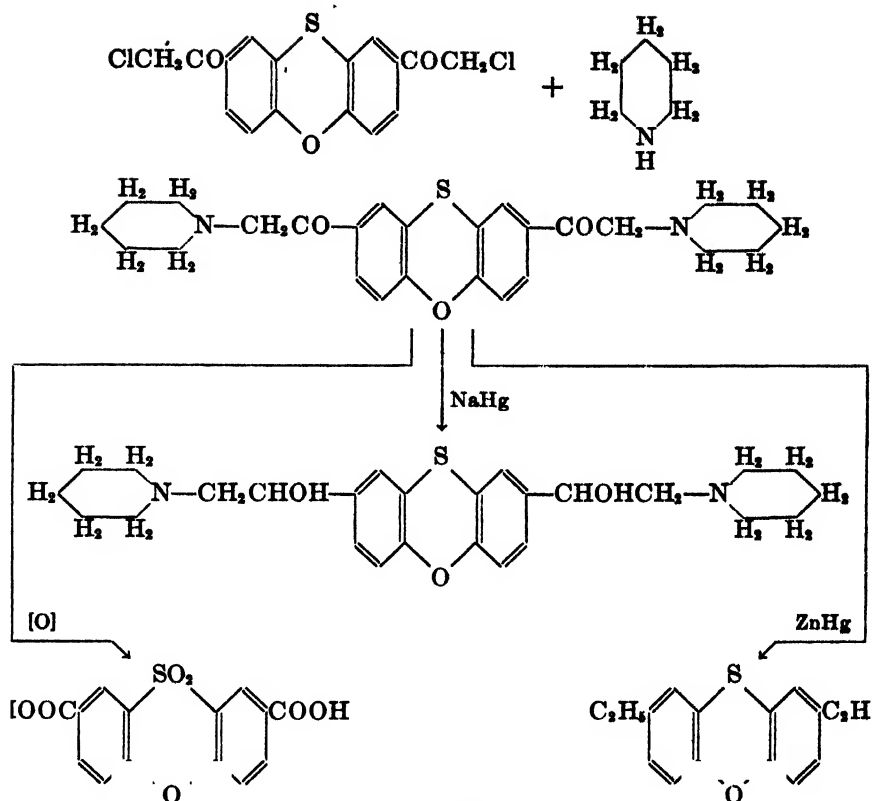
8. Benzoyl derivatives

A monobenzoyl derivative and a dibenzoyl derivative are known. By analogy with the corresponding acetyl compounds, Suter, McKenzie, and Maxwell (40) consider that they are probably the 2-benzoyl and the 2,8-dibenzoyl compounds. They are formed as a mixture when equimolar amounts of phenoxathiin and benzoyl chloride are refluxed in carbon disulfide with aluminum chloride:
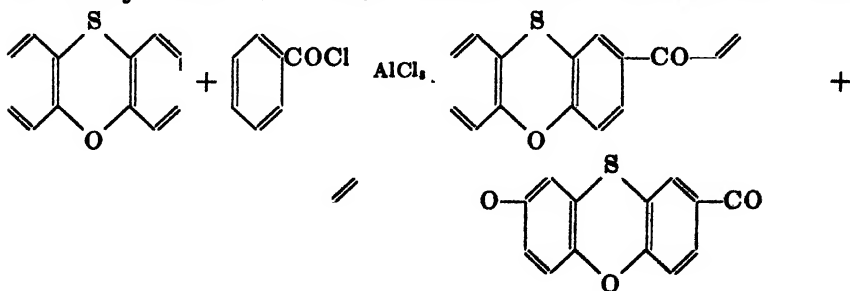
The monobenzoyl compound forms light yellow crystals, m.p. 96–97°C.; it is soluble in hot ethyl alcohol. The dibenzoyl compound, insoluble in ethyl alcohol, forms leaflets melting at 197°C.

9. Carboxylic acid derivatives

Bennett, Lesslie, and Turner (2) prepared a monocarboxylic acid derivative for use in a study of the configuration of the phenoxathiin nucleus. The acid was obtained by heating phenoxathiin with phenylethylcarbamyl chloride and anhydrous zinc chloride. It melted at 230–238°C., even after repeated recrystallization from aqueous alcohol or xylene. It was presumed to be either the 1-carboxylic or the 2-carboxylic acid, although the position of the carboxyl group was not determined.

The strychnine salt, with half a molecule of ethyl alcohol of crystallization, melts at 178–179°C.; the l-α-phenylethylamine salt melts at 188–189°C. Neither of these salts could be resolved into optical isomers.

Phenoxathiin-2-carboxylic acid, m.p. 260–262°C., was prepared by Suter, McKenzie, and Maxwell (40) in 8 per cent yield by treatment of the Grignard reagent from 2-bromophenoxathiin with carbon dioxide. They also obtained the crude 2-carboxylic acid in 60 per cent yield by oxidation of the 2-acetyl compound with bleaching powder.

Gilman, Van Ess, Willis, and Stuckwisch (11) obtained a yield of over 50 per cent of purified phenoxathiin-2-carboxylic acid (m.p. 260–265°C.) by the action of n-butyllithium on 2-bromophenoxathiin and treatment of the resulting 2-lithium compound with carbon dioxide:
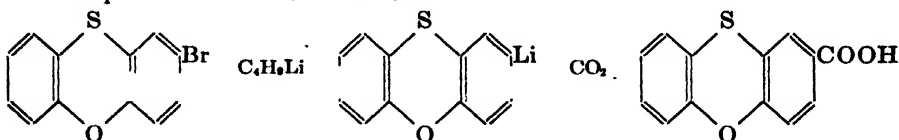
When metalation of phenoxathiin was carried out with phenylcalcium iodide, followed by carbonation, a compound melting at 260–262°C. was obtained. A mixed melting-point determination with an authentic specimen of phenoxathiin-2-carboxylic acid showed a depression, indicating that the metalation did not occur in the 2-position.

Mauthner (22) prepared phenoxathiin-3-carboxylic acid, m.p. 223°C., by the reduction of o,o'-dihydroxydiphenyl disulfide, followed by condensation with 4-chloro-3,5-dinitrobenzoic acid to form 1-nitrophenoxathiin-3-carboxylic acid. The nitro group was removed by reduction to the amino group, diazotization of the amino acid, and treatment of the diazonium compound with cuprous oxide.
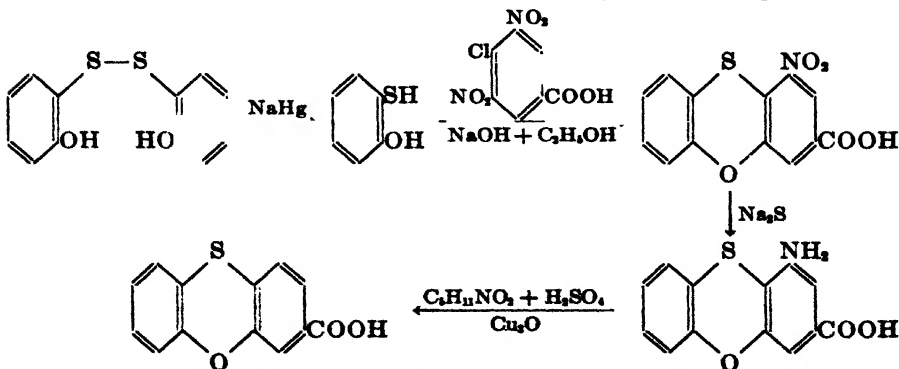
The acid forms phenoxathiin when heated with calcium oxide.

Phenoxathiin-4-carboxylic acid was prepared by Gilman, Van Ess, Willis, and Stuckwisch (11) by treatment of the 4-lithium derivative with carbon dioxide, as previously discussed in section 2. The crude acid, obtained in greater than 50 per cent yield, gave a melting point of 168–169°C. after three recrystallisations from acetic acid.

Phenoxathiin-10-dioxide-2,8-dicarboxylic acid, m.p. > 300°C., has been prepared by the oxidation of 2,8-diacetylphenoxathiin, 2,8-di(β-chloroacetyl)-phenoxathiin, and 2,8-dimethylphenoxathiin (42):
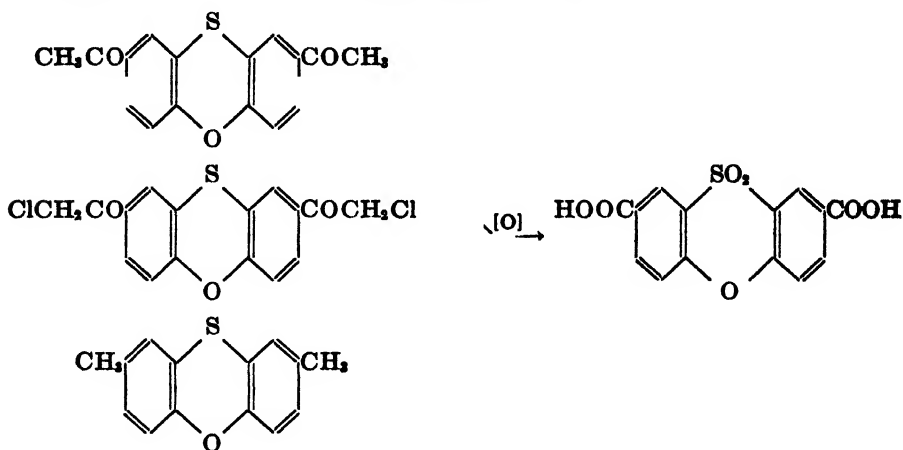
The methyl ester melts at 204–208°C.

10. Sulfonic acid derivatives

Only one monosulfonic acid derivative is known. Suter, McKenzie, and Maxwell (40) prepared phenoxathiin-2-sulfonic acid by the action of chlorosulfonic acid on an equimolar amount of phenoxathiin. It was isolated in 78 per cent yield as the crude sodium salt.

On refluxing the sodium salt with excess phosphorus oxychloride, the corresponding sulfonyl chloride was formed as a light yellow solid, m.p. 127–128°C. When warmed with concentrated ammonium hydroxide, the sulfonyl chloride was converted to colorless crystals of the amide, m.p. 177–178°C.
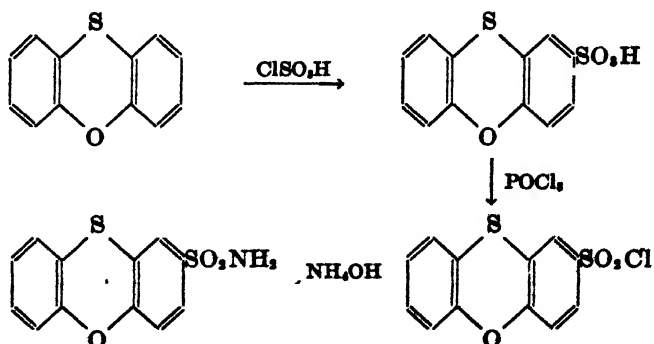
When phenoxathiin was heated with chlorosulfonic acid in a 1:4 molar ratio, phenoxathiin-2,8-disulfonic acid was isolated as the sodium salt. The silver salt was also prepared.

When the sodium salt was refluxed with phosphorus oxychloride, the disulfonyl chloride was formed as light yellow crystals, m.p. 142–143°C. This can also be prepared directly in 23 per cent yield by using phenoxathiin and chlorosulfonic acid in a 1:6 ratio. The positions in the phenoxathiin nucleus of the sulfonic acid groups in both the mono- and the di-sulfonic acids are established with a good degree of certainty, since the disulfonic acid can be transformed to the dichlorophenoxathiin of Hilditch and Smiles (15), which is probably the 2,8-dichloro compound.
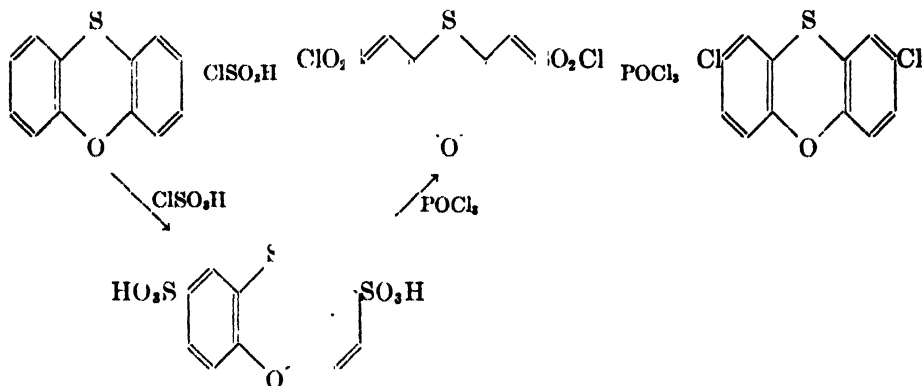
11. Organometallic derivatives

Gilman, Van Ess, Willis, and Stuckwisch (11) prepared the 4-lithium derivative by the action of n-butyllithium on phenoxathiin. The method of determination of the position of the entering lithium atom has already been discussed in section 2. The lithium compound is of particular importance because it gives a means of introduction of other substituents into the 4-position, which is otherwise inaccessible by direct nuclear substitution reactions.

Gilman, Van Ess, Willis, and Stuckwisch (11) also showed that phenoxathiin undergoes metalation with phenylcalcium iodide, but did not determine the position of the entering group.

Suter, McKenzie, and Maxwell (40) state that the Grignard derivative can be prepared directly from 2-bromophenoxathiin only slowly and with difficulty. Gilman, Van Ess, Willis, and Stuckwisch (11) report that the Grignard reagent can be readily prepared by the following reaction:
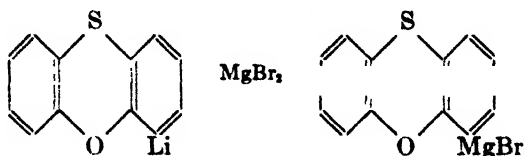
B. DERIVATIVES WITH MORE THAN ONE TYPE OF FUNCTIONAL GROUP

Several alkyl- and halogen-substituted phenoxathiins have been prepared. Drew (7) reports that 2-chloro-8-methylphenoxatellurin gives the corresponding phenoxathiin compound when heated with sulfur. Kent and Smiles (19) state that when 4-chloro-2-nitrophenyl 4'-hydroxy-*m*-tolyl sulfone is heated in alkaline solution longer than is necessary for rearrangement to 4-chloro-2-nitrophenyl-3'-sulfino-*p*-tolyl ether, the solution becomes turbid, owing to the separation of 2-chloro-8-methylphenoxathiin-10-dioxide,[2] m.p. 173°C.
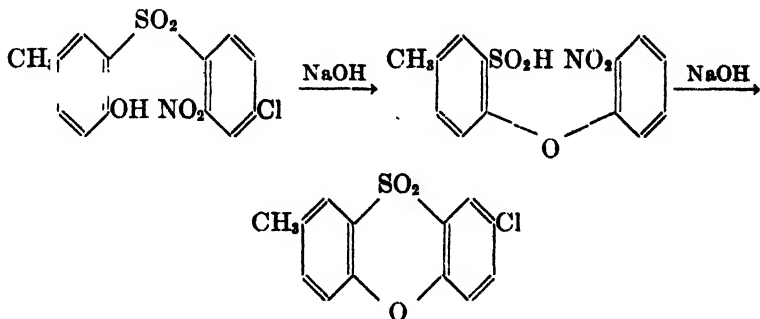
Methods of introducing alkyl and cycloalkyl groups into halogen-substituted phenoxathiins have already been discussed in section 1.

2-Nitro-8-chlorophenoxathiin was prepared as orange-yellow needles, m.p. 128–129°C., by treating 2-sulfino-4-nitro-4'-chlorodiphenyl ether with acetic anhydride and sulfuric acid. 2-Nitro-8-methylphenoxathiin, yellow needles, m.p. 156°C., was similarly prepared. Oxidation of 2-nitro-8-chlorophenoxathiin with chromic acid gave the 10-dioxide as colorless plates, m.p. 183–185°C. (20).
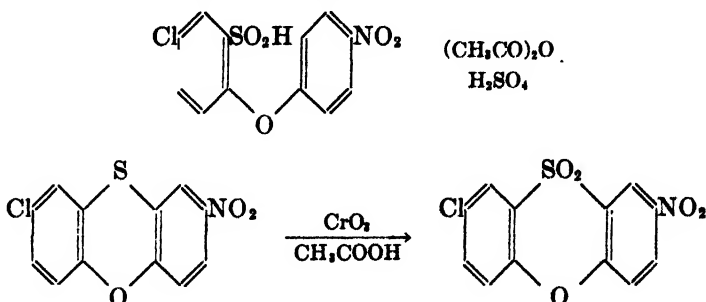
Mauthner (22) prepared orange-red crystals of 1-nitrophenoxathiin-3-carboxylic acid, m.p. 262°C., by reduction of *o*,*o*'-dihydroxydiphenyl disulfide, followed by condensation with 4-chloro-3,5-dinitrobenzoic acid (see section 9). Oxidation

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[2] The statement of Kent and Smiles that 3-chloro-8-methoxyphenoxathiin-10-dioxide is formed is obviously incorrect.

of 1-nitrophenoxathiin-3-carboxylic acid with chromic acid gives the 10-dioxide, m.p. 296–297°C.; with dilute nitric acid, the 10-oxide, m.p. 251–252°C., is obtained as light yellow needles. When 1-nitrophenoxathiin-3-carboxylic acid is reduced with sodium sulfide in aqueous alcohol, 1-amino-phenoxathiin-3-carboxylic acid is formed as colorless needles, melting at 250°C. with decomposition. The acetyl derivative, m.p. 294–295°C., is obtained by the action of acetyl chloride on the amino acid.

Bennett, Lesslie, and Turner (2) prepared 3-nitro-8-methylphenoxathiin-1-carboxylic acid by condensing 2-chloro-3,5-dinitrobenzoic acid and 3-thiol-*p*-tolyl carbonate in an aqueous alcohol solution of potassium hydroxide:
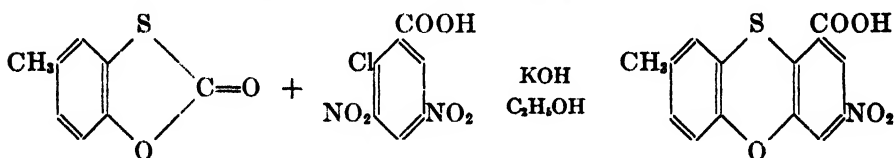
The crude acid was obtained in 40 per cent yield, and after crystallization from ethyl alcohol separated as orange clusters of slender needles, m.p. 253–254°C.

Several substituted phenoxathiin disulfides have been reported. Pollak and Riesz (27) state that 2,4-dithiolphenol forms an orange dipicryl derivative, m.p. 155°C., which, with alcoholic potassium hydroxide, forms 1,3,1′,3′-tetranitrodiphenoxathiin-8,8′-disulfide:
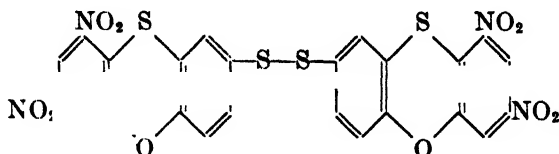

This compound decomposes explosively on heating, and is reduced by sodium sulfide to a dye which is light reddish brown on cotton.

Pollak and Riesz (26) also prepared what is probably 1,3,1′,3′-tetranitro-7,7′-dimethylphenoxathiin-8,8′-disulfide by heating with potassium hydroxide the orange-yellow dipicryl derivative of 4,6-dithiol-*m*-cresol:
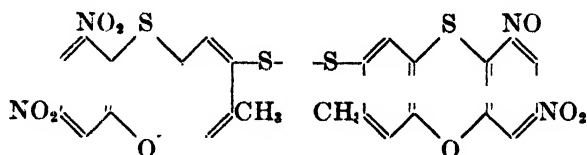

This dark red compound is reduced by sodium sulfide to a vat which dyes cotton a reddish brown.

Katscher and Lehr (18) prepared 1,3,1′,3′-tetranitro-7,9,7′,9′-tetramethylphenoxathiin-8,8′-disulfide by the action of picryl chloride in alcoholic potassium hydroxide solution on 2,4-dithiol-1,3,5-xylenol:
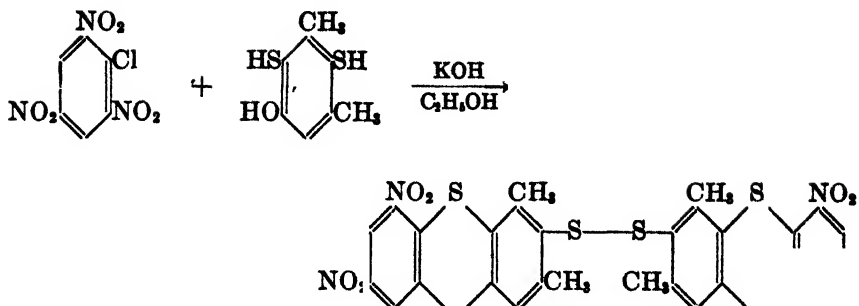
It forms dark red crystals, melting at 255–257°C.

The structure of 3,7-diphenyl-1,9-diketo-1,2,3,4,6,7,8,9-octahydrophen-oxathiin-10-oxide has been provisionally assumed by Desai and Wali (5) for the product, $C_{24}H_{20}SO_4$, m.p. 216°C., obtained by the condensation of phenyldihydro-resorcinol with thionyl chloride:
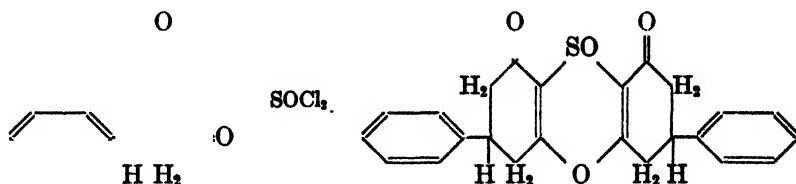
Similarly, the condensation of dimethyldihydroresorcinol and thionyl chloride is assumed to yield the corresponding 3,3,7,7-tetramethyl-1,9-diketo-1,2,3,4,6,7,8,9-octahydrophenoxathiin-10-oxide, $C_{16}H_{20}SO_4$, m.p. 181–182°C.
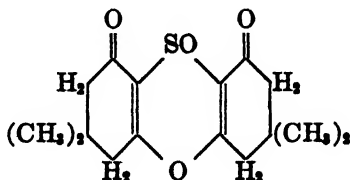

Pollak, Riesz, and Riesz (28) prepared 1,4-diketo-2-chloro-3-(3'-methyl-4'-hydroxy-5'-thiolphenyl)thiol-6-methyl-8-thiolphenoxathiin by warming 3,5-dithiol-o-cresol with chloranil in alcoholic solution:
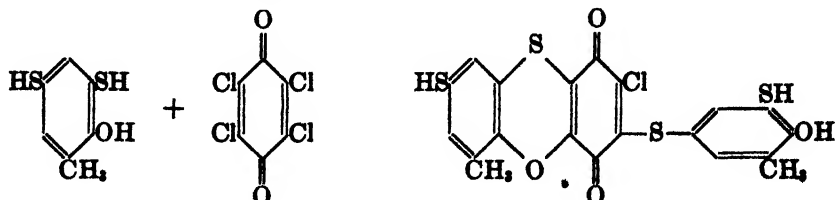
It is a brown solid, decomposing at 250°C. without melting.

4,6-Dithiolresorcinol gives a yellow dipicryl derivative, which yields with potassium hydroxide a tetranitrodiphenoxathiin derivative (26):
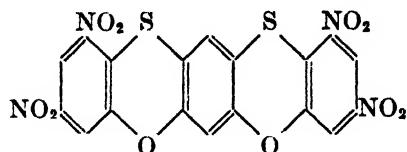
This substance is dark red and decomposes above 280°C.

Pollak and Riesz (26) report that dimercapto-*o*-cresol forms an orange-red dipicryl derivative, which, when treated with alcoholic potassium hydroxide, yields a phenoxathiin derivative.

It is reported (3) that phosgene reacts with phenoxathiin compounds containing amino, halogen, and sulfonic acid groups, substituted ureas being formed. A similar reaction occurs with the halide or anhydride of carbamic acid.

V. STEREOCHEMISTRY

Higasi and Uyeo (13, 14) determined the dipole moment of phenoxathiin in benzene and in cyclohexane solutions to be 1.09 Debyes. They concluded that the phenoxathiin molecule is folded about the line joining the heterocyclic atoms. They predicted, however, that, since the activation energy of racemization would be at most a few kilogram-calories, no optical isomerism is to be expected in phenoxathiin derivatives.

This prediction was verified by Bennett, Lesslie, and Turner (2), who failed to resolve either 3-nitro-8-methylphenoxathiin-1-carboxylic acid or phenoxathiin-2(or 1)-carboxylic acid. The non-resolvability of phenoxathiin derivatives has also been attributed to the fact that there is only a slight tendency to stable folding, owing to the insufficient dissimilarity in size of sulfur and oxygen (41).

Cullinane and Rees (4) studied isomorphous relationships between phenoxathiin, phenothiazine, phenoxazine, and diphenylene dioxide. Assuming that the ability of binary mixtures of substances to form solid solutions is the criterion of isomorphism, and that similarity in molecular configuration is the reason for isomorphism, they conclude that phenoxathiin has a folded structure. This conclusion was also based on a calculation using the valence angles and atomic radii of the atoms in the phenoxathiin molecule. From measurements of the axial ratios and from x-ray observations, Wood, McCale, and Williams (44) showed that phenoxathiin, phenothiazine, phenoxaselenin, and phenoxatellurin are isomorphous. They concluded that the phenoxathiin molecule is folded, and tabulated suggested angles of fold. Magnetic measurements were consistent with the structure proposed.

VI. USES

A rather large number of uses have been proposed for phenoxathiin and some of its derivatives.

Many of these uses are due to the harmful action of phenoxathiin on some of the lower forms of life. It was found, for example, to show marked bacteriostatic

action on *Streptococcus hemolyticus* (oyler strain) and on *Streptococcus hemolyticus epidemicus* and considerable inhibition of *Streptococcus viridans* at a level of 100 parts per million of peptone broth (8). Halogen-substituted phenoxathiinureasulfonic acids have been recommended as bactericides and fungicides (3).

A slight anthelmintic effect against *Haemonchus contortus* was shown by phenoxathiin in 0.25 g. doses per kilogram of body weight of sheep, and larval development in fecal cultures was prevented. Doses of 0.5 g. per kilogram were fatal, and doses of 0.15 g. per kilogram were ineffective (12).

Fink and Vivian (10) have shown that phenoxathiin kills 50 per cent of mosquito larvae in 16 hr. at a concentration of 2 parts per million.

Phenoxathiin has been tested as a stomach poison against larvae of *Phlyctaenia rubigalis* and found to be more toxic than lead arsenate (23). Smith, Siegler, and Munger (30, 36) found that phenoxathiin was outstanding in initial toxicity against codling-moth larvae, but that it loses much of its effectiveness when exposed as a spray deposit for a week or more. Halogen-substituted phenoxathiinureasulfonic acids, which are fast to washing and fulling, have been recommended to protect wool against moths (3).

Various alkyl- or cycloalkyl-phenoxathiins, their oxides and dioxides, and their halogen derivatives are recommended for use as insecticides in dusts or sprays (31, 32, 33, 34).

The oxides and dioxides of cycloalkylphenoxathiins and their halogen derivatives have also been recommended as modifiers in plastic materials or as intermediates (34). Smith and Moll state that alkylphenoxathiins and their halogen derivatives can be used as modifiers in plastic compositions, as intermediates, as antioxidants, and as rubber and gum inhibitors (31, 35).

Pollak and Riesz (26, 27) state that the products obtained by the reduction with sodium sulfide of 1,3,1′,3′-tetranitrodiphenoxathiin-8,8′-disulfide and 1,3,1′,3′-tetranitro-7,7′-dimethylphenoxathiin-8,8′-disulfide are reddish brown dyes on cotton.

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THE STRUCTURE OF FIBROUS PROTEINS[1,2]

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Following a presentation of some of the more important general principles which can reasonably be assumed to apply to protein structures, models have been proposed and compared with x-ray and analytical data for silk fibroin (*Bombyx mori*), β-keratin, α-keratin, and collagen.

The problem of the determination of the arrangements of atoms in proteins is an exceedingly difficult one. Even if we bring to bear the very powerful techniques now available, such as those involving the use of x-rays, the electron microscope, and the ultracentrifuge, there seems to be little hope of solving the problem in the near future by *deductive* methods alone. The most promising method of attack at this stage seems to require the making of tentative assumptions regarding the structures of protein molecules, followed by experimental testing of these assumptions. To avoid waste effort we should of course be guided in making these assumptions by such knowledge as is already available regarding related structure and by such limitations as are imposed by deduction from experimental data on the proteins themselves.

This is the point of view which will be taken in this paper. Starting with certain assumptions which appear reasonable on the basis of analogy or for which there is direct experimental evidence, we shall speculate regarding possible types of structure for proteins and then, where possible, test our speculative pictures by means of available applicable data.

For the present, we shall limit our discussion to *fibrous* proteins.

ASSUMPTIONS AND GENERAL PRINCIPLES

We shall assume, following Emil Fischer, that fibrous proteins are built up, at least primarily, of long polypeptide chains or very large rings. We shall assume these chains to be composed of the "residues" of amino acids, at least approximately in the relative proportions determined by accepted analytical methods. We shall assume, as is customary, that the orientation of the bonds around each asymmetric α-carbon atom is uniformly *levo*—that is, the same as in levolactic acid.

[1] Communication No. 889 from the Kodak Research Laboratories, Rochester, New York.

[2] Presented (except for minor changes) under the title "Hydrogen Bonds in Proteins" at the Symposium on "The Hydrogen Bond and Related Topics" at the Memphis Meeting of the American Chemical Society, April 21, 1942. An outline of the material herein was included in the author's recent review of "X-ray Studies of the Structure of Compounds of Biochemical Interest" in the 1942 Annual Review of Biochemistry (36). The structure models described in this paper have also been briefly discussed at previous meetings of the American Chemical Society (September, 1937; April, 1939; April, 1940) and at the Gibson Island Conference on X-ray and Electron Diffraction, July, 1940.

We shall make the reasonable assumption that the distances between closest atoms and the angles between adjacent bonds are in proteins approximately the same as in comparable small molecules of known structure (table 1). We shall also assume that the attraction between CO and NH groups which has been found to produce intermolecular NHO bridges in all the comparable small molecule crystals of known structure is also effective in producing similar (intermolecular and intramolecular) bridges in proteins. Because of the resulting

TABLE 1*

Interatomic distances and interbond angles

Experimental values for three simple compounds and estimated values for proteins

|	DIKETO-PIPERAZINE (25)	GLYCINE (4)	ALANINE (41)	PROTEINS
	Å.	Å.	Å.	Å.
N—C	1.41	1.39	1.42	1.41
C—C′.	1.47	1.52	1.54	1.52
C′—O.	1.25	1.25, 1.27	1.23, 1.25	1.25
C′—N	1.33			1.33
N—H···O	2.85	2.76, 2.83	2.78, 2.81, 2.88	2.85
	degrees	*degrees*	*degrees*	*degrees*
∠NCC′. .	120	112	112, 113	112
∠CC′O . .	120	119	118	118
∠C′CR ..			110	110
∠OC′O . .		122	124	
∠CC′N. ...	120			118
∠C′NC	120			118

*C in this table refers to a carbon atom of a CHR or CH₂ group; C′ refers to a carbon atom of a carbonyl group.

increased stability, we expect these bridges to be linked together in long chains or in rings capable both of resonance of the following sort
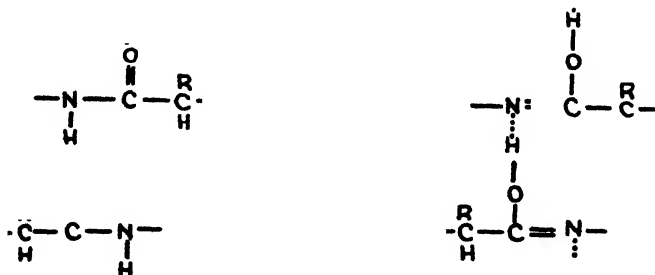
and of synchronized oscillations of the hydrogens and the mobile electron systems (23). That NHO bridges actually are present in quantity in proteins has been confirmed by infrared spectrum studies (15, 23). These studies show that OHO bridges, if present at all, are present only in very small amounts.

Since most of the amino acid residues in proteins contain a hydrogen atom attached to the α-carbon atom, and since it might be expected that such a hydrogen would be capable of shifting to the neighboring oxygen, we should perhaps consider resonating structures of this sort:
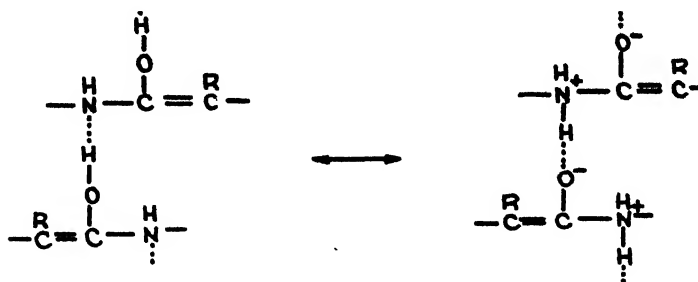
For the present, however, we shall neglect such a possibility.

The hydrogen atoms of the CHR groups may also form bridges to carbonyl oxygen atoms, since there is good evidence for C—H···O bridges in comparable structures (24, 28, 30, 32, 34, 54, 60). This possibility will be discussed below in connection with the structure of collagen.

A protein which gives an x-ray diffraction pattern showing lines or spots instead of, or in addition to, the broad ill-defined bands characteristic of liquids and truly amorphous solids, must possess, over large regions at least, a regular crystalline type of structure. Polypeptide chains extending through the crystalline regions must each have a screw axis of symmetry, or else two or more chains must be grouped around screw axes or other symmetry elements. The unbalanced forces on opposite sides of a chain which has no screw axis—e.g., any of the earlier chain structures advocated for α-keratin by Astbury (13, 14, 29) or the one that he has most recently proposed (7, 10) for collagen—would tend to bend it continuously in the same direction. Fibrous proteins giving crystalline x-ray patterns can have layer structures composed of unsymmetrical chains only if the chains in each layer are alternately oriented in opposite directions, in such a way as to give a symmetry axis or symmetry plane or a set of symmetry centers between adjacent chains.

A principle which is logically reasonable and which has been amply verified by structure analyses of a great many substances is that like atoms or atomic groups tend to be surrounded in a like manner. Because of the variety of R groups present in any given protein, some differences between the environments of corresponding groups must be expected, but these differences should be minor ones. In general, a structural pattern for a protein in which like groups are all surrounded in a like manner, except for differences between the R groups, is more probable than one in which this is not the case. This is an argument against all of the structures advocated by Astbury for α-keratin (8, 11, 13, 14, 29) and against his latest collagen model (7, 10).

Another important structure principle is that of *close-packing*. In addition to the attractive forces connected with covalent-bond and hydrogen-bridge

formation and the Coulomb and polarization forces acting when one (or both) of two atoms or groups of atoms possesses a net electrical charge, two atoms or groups attract each other by what we may call a "van der Waals attraction" and repel each other by an "interpenetration repulsion," having a magnitude depending on the amount of interpenetration of the "electron clouds" of the two atoms or groups (figure 1). Both of these forces increase in magnitude as the distance decreases, but the interpenetration repulsion increases more rapidly. At distances greater than a certain minimum, characteristic of the kinds of atoms or groups, the net force is an attraction; at smaller distances, it is a repulsion.
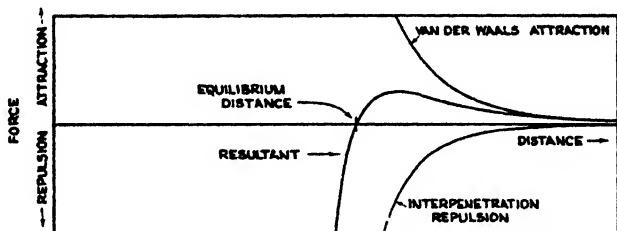
Fig. 1. Illustrating the variation with the distance between two atoms of their mutual van der Waals attraction and interpenetration repulsion forces and of the resultant force.

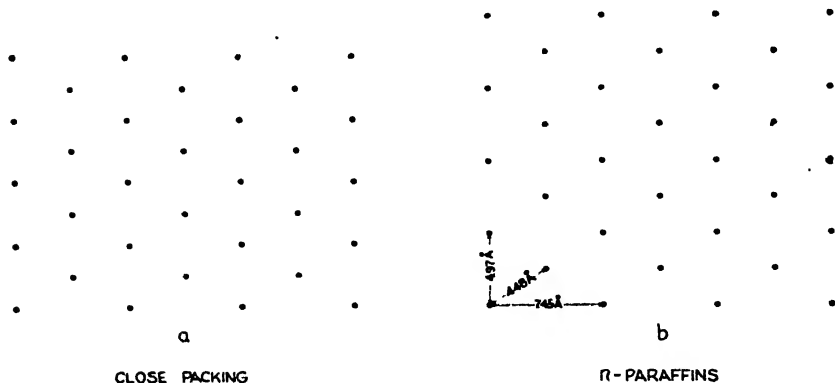CLOSE PACKING   n - PARAFFINS

Fig. 2. (a) Close-packing of spheres having their centers in a plane; (b) distribution of chain axes in a normal paraffin crystal.

From these considerations it follows that, other things being equal, the most stable arrangement for an assemblage of molecules is one in which the component atoms and groups are packed together so that (a) the distances between neighbors are close to the equilibrium distance, (b) each atom or group has as many close neighbors as possible, and (c) there are no large unoccupied regions. In other words, each structure tends to be as "close-packed" as possible, consistent with the "sizes" of its component atoms or groups. Like spherical atoms or groups in a single plane thus assume a hexagonal arrangement (figure 2a) in which each has the maximum number (six) of close neighbors, all at the same distance. With non-spherical atoms or groups a similar arrangement, but dis-

torted, is produced. In a crystal of a paraffin or of one of its simple derivatives, the chain axes line up parallel to each other in the same sort of hexagonal array (but usually distorted). In normal long-chain paraffins (37, 49), for example, each chain axis has four others around it at a distance of 4.48 Å. and two at a distance of 4.97 Å. (figure 2b).

We shall now consider various types of hypothetical structures conforming to the foregoing assumptions and general principles and see which satisfy best the requirements of the x-ray data for certain fibrous proteins.

EXTENDED ZIGZAG CHAIN STRUCTURES

If a polypeptide chain, having bond distances and bond angles as given in the last column of table 1, is extended as much as possible, a zigzag structure results, in which all of the chain atoms (C, C', N) and the carbonyl oxygen atoms lie in one plane; the H atoms of the CHR groups (and probably also those of the

TABLE 2

Approximate distances in certain structures

	PARALLEL TO FIBER AXIS		PERPENDICULAR TO FIBER AXIS	
	Identity distances if R's all equivalent	Average distance per residue	Between chains	Between layers
	Å.	Å.	Å.	Å.
Extended chain (calculated)	7.2	3.6	4.5	
Silk..	7.0	3.5	4.5	9.2
β-Keratin...	6.7	3.33	4.65	9.7
α-Keratin.........................	10.3	1.7	9	9.8
Collagen	5.7	2.9	4.4	11

NH groups) and the nearest carbon atoms of the R radicals, on the other hand, do not lie in this plane. If all of the residues have a levo-configuration, the C—R bonds extend alternately above and below the plane of the zigzag.
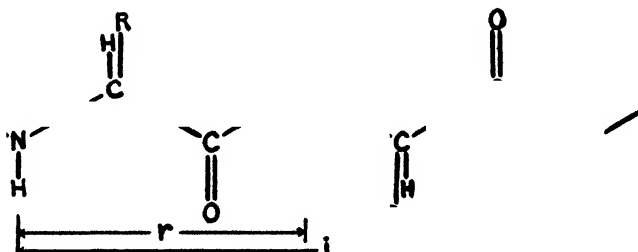

The distance *r* per residue in the direction of the chain axis is about 3.6 Å.; the identity distance *i* (neglecting differences in the R radicals) is twice this length.

X-ray data from silk fibroin (21, 31, 39, 40, 43, 44, 45, 51, 52, 56) and from β-keratin (12, 13) (stretched hair, horn, quill, fingernails, etc.) show apparent identity distances (table 2) in the direction of the fiber axis from 6.7 Å. to 7.0 Å.,

and it has been assumed (12, 47, 48), justifiably, that these substances are composed of polypeptide chains which are nearly fully extended.

Reasoning from the principles outlined above, one would expect fully extended polypeptide chains in a protein to line up in sheets, with their chain axes parallel and with the hydrogen atom of each NH group linked to the oxygen atom of a CO group in the adjacent chain by means of an NHO hydrogen bridge, in this manner:
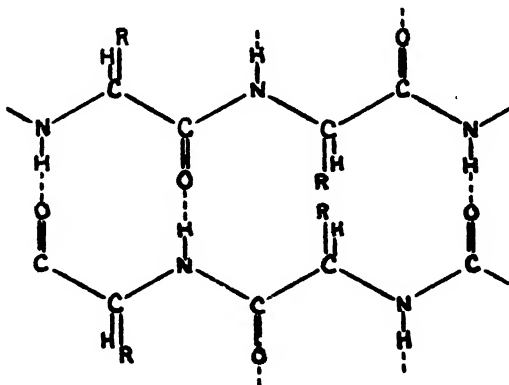
Although the x-ray data from silk and β-keratin cannot at present be said to prove that this hypothetical type of structure is correct, they seem to be in agreement with it, as will be shown below.

It may be noted that this structural arrangement permits the long-chain resonance and synchronized oscillations which, as has been pointed out above, make the hydrogen bonds especially stable. The other extreme resonance structure can be represented formally in the following way:
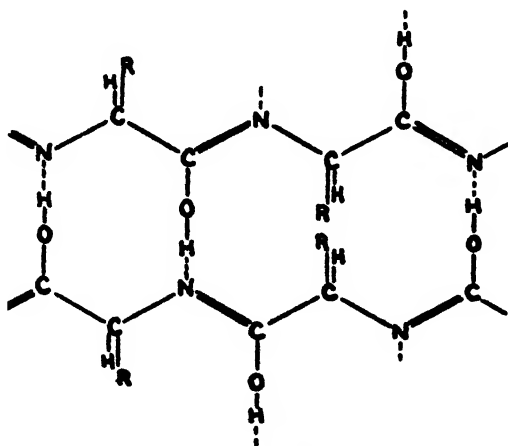
These formulas are somewhat idealized. For example, it is probable that the zigzag chains and the hydrogen bridges connecting them are not coplanar.

According to the Lewis theory of valence (42), corroborated by much experimental evidence on the structures of small molecules, the NH bonds in structure A should not be in the plane containing the centers of the nitrogen atom and the two carbon atoms to which it is bonded.   Also, the C—O and O—H bonds in structure B and the C=O and O···H bonds in structure A should not be colinear.   Moreover, coplanar zigzag chains would require the R groups attached to adjacent chains to be too close together.
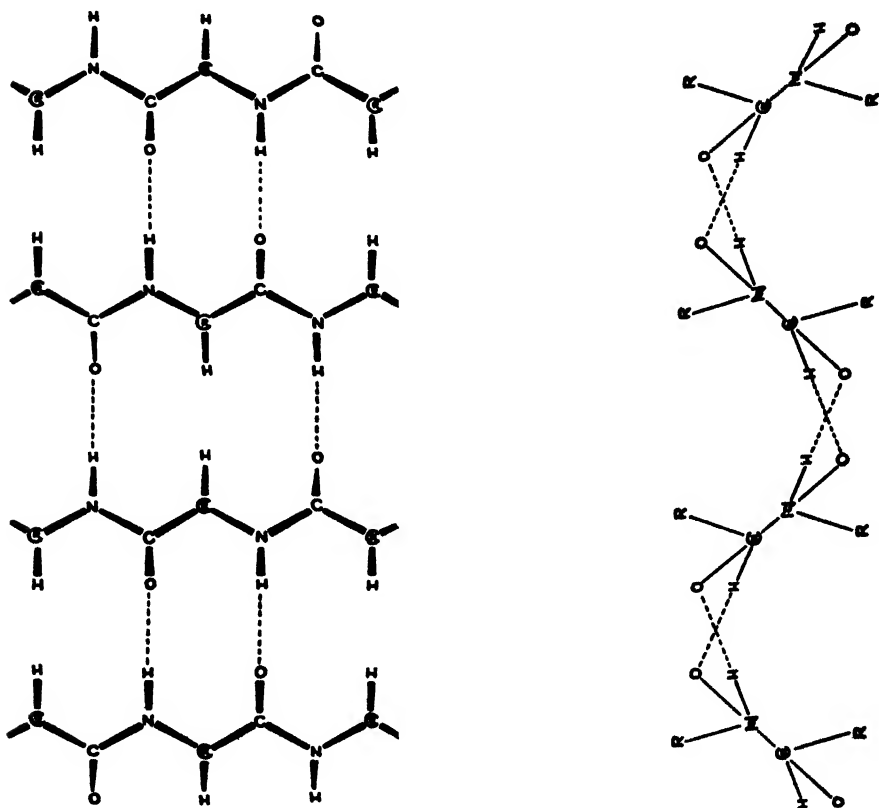

FIG. 3. Two views of a hypothetical structure pattern for a layer of extended polypeptide chains.

Figures 3 and 4 represent two structures (35) to which the foregoing objections do not apply.   The latter seems less reasonable than the former, since, assuming a like (levo) configuration around each asymmetric carbon atom of a CHR group, the R groups of alternate chains are differently situated.   The C—R bonds in half of the chains are approximately normal to the median plane of the layer. Those in the other half of the chains are so oriented as to place the first carbon atom of the R group only about 3 Å. from a carbon atom in the neighboring

chain. This is somewhat closer than the expected equilibrium distance (3.6–4.0 Å.). Only if all the "R groups" in half of the chains were hydrogen—i.e., if all of the residues in these chains were glycine residues—would the structure of figure 4 seem to be satisfactory.

The bond distribution shown in figure 5 should also be considered. Here the sequence —NH·CHR·CO— runs in the *same* direction for all the chains; in
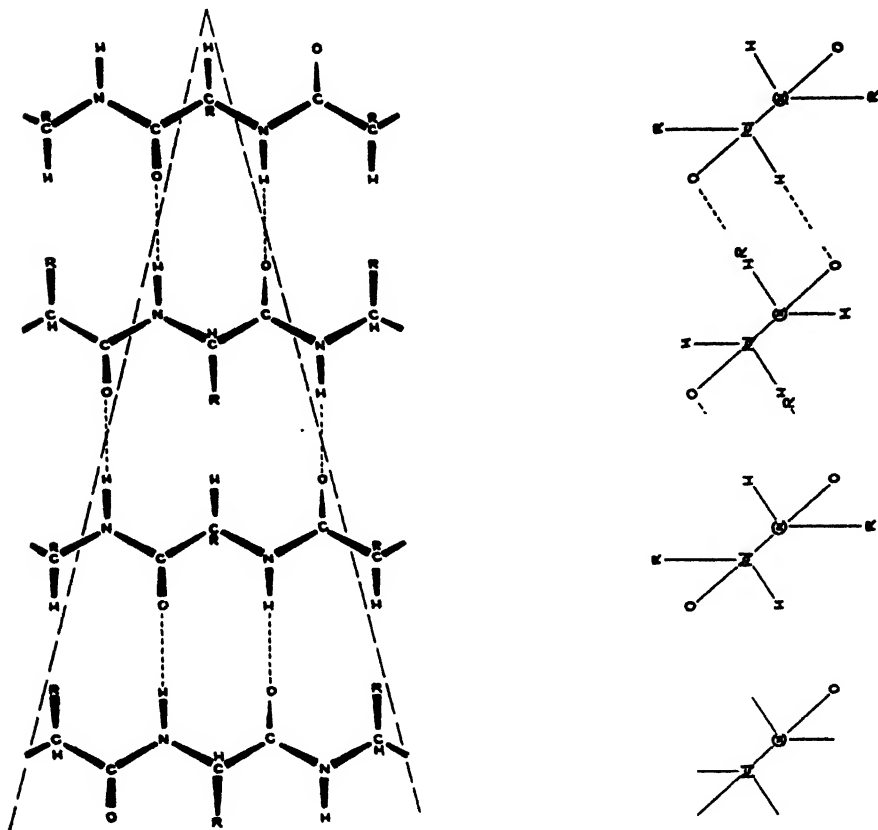

FIG. 4. Two views of another hypothetical pattern for a layer of extended polypeptide chains.

the structures of figures 3 and 4, *alternate* chains run in opposite directions.[3] The hydrogen bridges would tend to straighten out, causing the chains to coil up to some extent. This pattern therefore seems improbable for proteins in which the x-ray data show the chains to be practically fully extended.

For chains which are not fully extended, we should also consider structures

[3] In reference 35 it was incorrectly stated that the sequence is the same for all chains in the structure of figure 4.
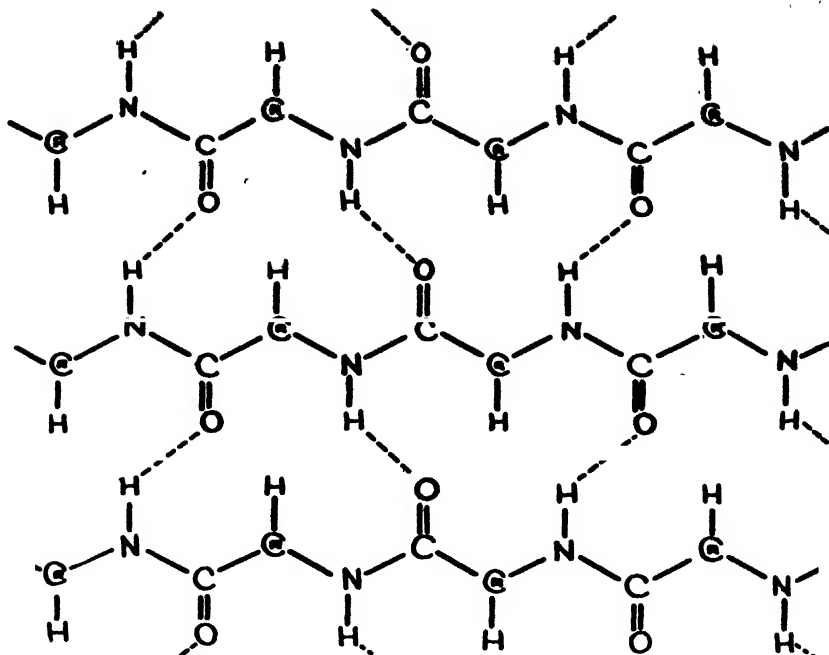
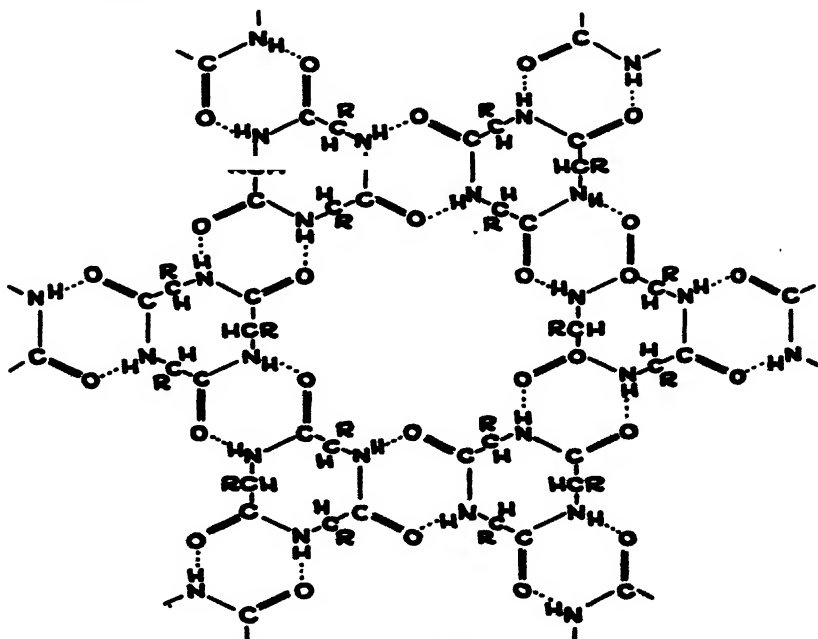Fig. 5. Bond distribution in another hypothetical structure for a layer of extended polypeptide chains.

Fig. 6. Projection, on a plane normal to the axes of the spirals, of a hypothetical structure composed of spiral polypeptide chains, connected to one another through NHO bridges.

like those of figures 6 and 7, in which each chain spirals in such a way that it is connected by NHO bridges to *three* or more others, instead of just to *two*, as in the layer structures just described. Without entering into a detailed discussion of these structure patterns, we shall merely state here that for silk, α-keratin, β-keratin, and collagen they seem less likely, on the basis of the x-ray data, than the structures which will be described.
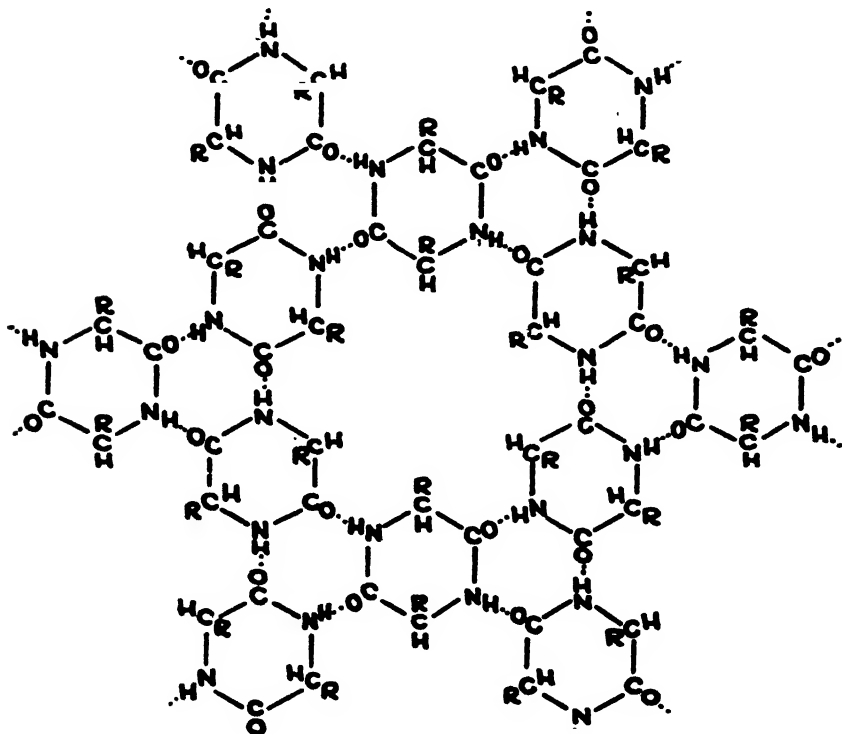

Fig. 7. A projection of another hypothetical structure composed of spiral polypeptide chains, linked together through NHO bridges.

SILK FIBROIN

The x-ray studies of silk fibroin show that there are at least two kinds, having structures which are definitely different. The best and most complete x-ray data are from the type known as *Bombyx mori*; its structure will be that considered here.

Determinations of the composition of silk (2, 19, 46, 57) show (table 3) that approximately half of the residues are glycine (R = H) and about one-fourth are alanine (R = CH$_3$). Meyer and Mark (46, 47, 48) suggest that the substance consists of a crystalline portion, in which glycine and alanine (or alanine *plus* serine) residues are present in equal numbers, and an amorphous portion com-

TABLE 3

Approximate compositions of silk fibroin, keratin, and collagen

AMINO ACID		RESIDUE FRACTIONS		
		Silk fibroin	Wool keratin	Collagen
Glycine	H | —NHCHCO—	0.49	~⅓	0.33
Alanine....	CH₃ | —NHCHCO—	0.25		0.09
Tyrosine	CH₂C₆H₄OH | —NHCHCO—	0.05		
Leucine.	CH₂CH(CH₃)₂ | —NHCHCO—	0.016	~⅛	0.05
Isoleucine	CH(CH₃)CH₂CH₃ | —NHCHCO—			
Serine	CH₂OH | —NHCHCO—	0.014	~⅛	
Cystine + 2.	CH₂S— | —NHCHCO—		~⅛ (or ⅙)	
Glutamic acid...... ..	CH₂CH₂COOH | —NHCHCO—		~⅛	
Proline..	CH₂ H₂C CH₂ | | —N——CHCO—			0.14
Hydroxyproline........	CHOH H₂C CH₂ | | —N——CHCO—			0.10

posed of glycine residues and residues of all the other amino acids present.   The argument for this is not very strong, however.   Since about 15 per cent of the

residues are still unknown, it seems best, for the present, to consider silk fibroin as composed of equal numbers of glycine residues and of other residues, treating these others as if they were all alanine, but realizing that many of them are not.

Kratky and Kuriyama (39, 40) were able to account satisfactorily for the locations of all of their x-ray reflections from *Bombyx mori* on the basis of any one of the (pseudo) unit cells listed in table 4. A, B, C, D, E, and F in this table correspond to Kratky and Kuriyama's cells I, II, VIII, X, V, and VI, respectively. Their dimensions have been changed to those of the equivalent units having the interaxial angle nearer 90°. Their designations *a*, *b*, *c*, and *γ* have also been changed to *c*, *a*, *b*, and *β*, respectively. The probable error of each of the unit distances is perhaps 0.2 to 0.3 Å. (McNicholas (45) gives 7.04 Å. as the mean value of *b*, computed from twenty-two different diffraction photographs.) The length *b* is the (pseudo) identity distance in the direction of the fiber axis; *a* probably lies in the layer plane; *c* sin *β* is the perpendicular distance between layer planes, about 9.16 Å. in each case.[4]

TABLE 4

Dimensions of possible unit cells for silk fibroin (Bombyx mori), according to Kratky and Kuriyama

	a	b	c	β	NUMBER OF RESIDUES
	Å	Å	Å.		
A .	4.72	6 95	9.25	86° 10'	2
B	4 95	6 95	9.15	89° 26'	2
C	4 60	6 95	9.26	81° 39'	2
D	17 71	6 95	9 75	70° 1'	8
E .	8 92	6 95	9.40	76° 40'	4
F .	8.98	6 95	9.37	77° 43'	4

A structure for silk fibroin consisting of layers of the type of figure 4, with alternate chains within each layer composed entirely of glycine residues, seems to be ruled out by the identification (1) of the dipeptides *d*-alanylglycine and glycyl-*l*-tyrosine.

Unit cells A, B, and C can be ruled out as improbable on several counts, the most important being that they would require all chains to be oriented in the same way. Assuming an extended zigzag chain, with glycine and other residues alternating, all of the C—R bonds would extend on the same side of the plane of the zigzag in all of the chains. There would be no symmetry elements in the structure whatever. All the chains and all of the layers would tend to bend continuously in the same direction. With a structure of this sort, silk would give x-ray diffraction photographs characteristic of amorphous materials.

[4] Meyer and Mark (48) state that Herzog and Kratky, in a private communication, give as the simplest possibility a unit cell having the following dimensions: 8.80 Å., 7.00 Å., 9.68 Å., 75° 50'. Since Meyer and Mark's book was apparently published early in 1930—the preface is dated May, 1930—whereas the Kratky and Kuriyama paper was not received for publication until October 25, 1930, we may assume that these (Herzog and Kratky) dimensions were superseded by those given by Kratky and Kuriyama.
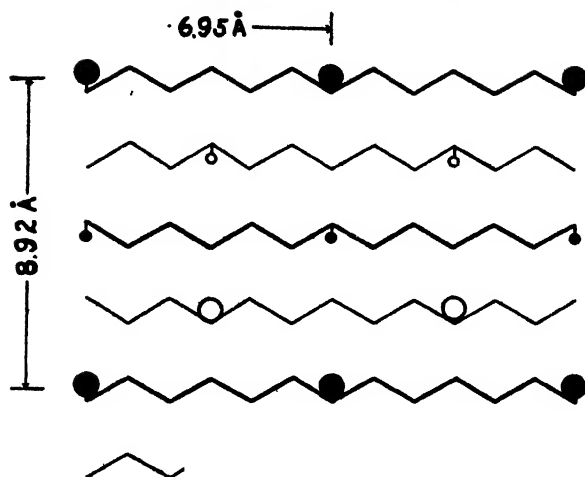
FIG. 8. Structure E for silk fibroin, assuming the layer structure of figure 3. The relative positions of the zigzag chains in two adjacent layers (heavy lines, lower layer; light lines, upper layer) are shown, with the positions of those R groups (large circles) and H atoms (small circles) of the CH_2 groups in the glycine residues which lie between the median planes of the two layers.
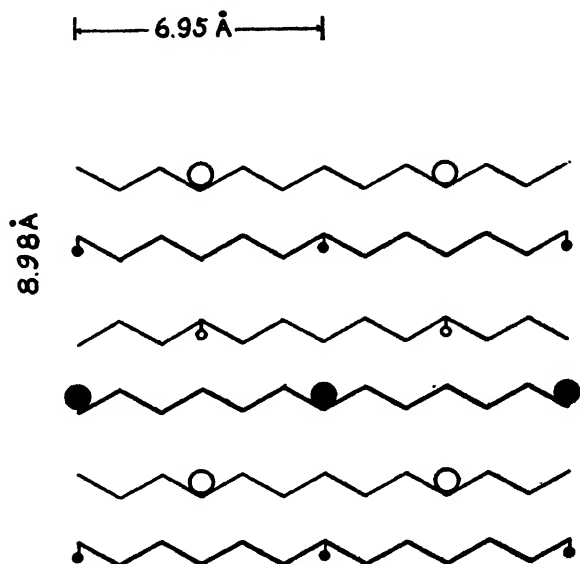

FIG. 9. Structure F for silk fibroin, assuming the layer structure of figure 3. This shows the relative positions of the chains in two adjacent layers, with the disposition of R groups and H atoms between these layers.

Another argument against the A, B, and C units is that, with glycine and other residues alternating in each chain, 010 reflections should be observed, whereas none have been reported.

Still another argument against the A, B, and C units is that the *a* distance in each is only about half the minimum possible value for a structure of the type of figure 3, and the *b* distance is close enough to that calculated for fully extended chains to make a bond distribution like that depicted in figure 5 improbable. Moreover, the chains in adjacent layers would be nearly over and under each other, giving an unreasonable packing of R groups and H atoms between layers.

The unit cell D gives a similar unlikely distribution between the layers.

Units E and F seem much more reasonable   Assuming a structure of the type shown in figure 3, with the C—H and C—R bonds tilted as indicated in the projection on the right-hand side of that figure (the angle of tilt being somewhat arbitrary), the interlayer distribution of H atoms and R groups (mainly CH_3) is as shown in figures 8 and 9. Both of these appear reasonable. A decision between them does not seem possible at the present time.

β-KERATIN

As Astbury has pointed out (6, 13), x-ray photographs of β-keratin are similar, as regards their major features, to those of silk fibroin.

With the meager x-ray data obtainable, a good direct determination of the dimensions and symmetry of even a pseudo unit cell (i.e., the true unit if all the R groups were alike) is not possible. Astbury states, however, that his data can be accounted for on the basis of an orthogonal cell of the following dimensions:

$$a = 9.3 \text{ Å.}; b = 6.7\text{-}6.8 \text{ Å.}; c = 9.8 \text{ Å.}$$

Tentatively, we may accept these. Assuming layers of the figure 3 type, as in silk, *b* is the length of two residues in the direction of the chain axis, *a* is twice the distance between adjacent chain axes in each layer, and *c* is the average distance between layers. The larger value of *c* and the smaller value of *b* than in silk may reasonably be attributed to the larger average size of the R groups.

This unit cell places the chains in adjacent layers directly over or under each other, rather than shifted as shown in the structures deduced for silk (figures 8 and 9), but the x-ray data from β-keratin can hardly be said to prove this point. If Astbury is correct about this, the chain-over-chain arrangement may be a result of cystine (and perhaps other) bridges between chains in different layers.

From known interatomic distances (33, 50) and the assumption of tetrahedral bond angles ($\sim 109.5°$), one can compute a maximum distance of 8.0 Å. between two chain axes joined by a cystine radical. This is perhaps not in too poor agreement with the observed average interlayer distance of 9.8 Å., since the variety of R groups doubtless produces large distortions from the idealized structure models represented in the figures and since the bond angles may be somewhat larger than the tetrahedral angle.

Another alternative which appears more reasonable is that the cystine radicals

bridge between adjacent chains *in the same layer*. The calculated distance for this (~ 4.7 Å.) is in good agreement with the experimental distance (4.65 Å.) between chain axes.

Interchain bridges need not be limited to hydrogen bridges and cystine bridges. There may also be amide or ester linkages, for example, such as could be formed by condensation between serine and glutamic acid. From the analytical figures (3, 5, 8, 11, 22, 58), approximately one-ninth of the residues are serine, one-ninth are glutamic acid, and one-ninth are "cystine + 2." (Each cystine molecule obtained in the analysis comes from two "cystine + 2" residues.) It seems reasonable to guess that there is a cystine or serine–glutamate bridge connecting each chain to its immediate neighbors at every third residue

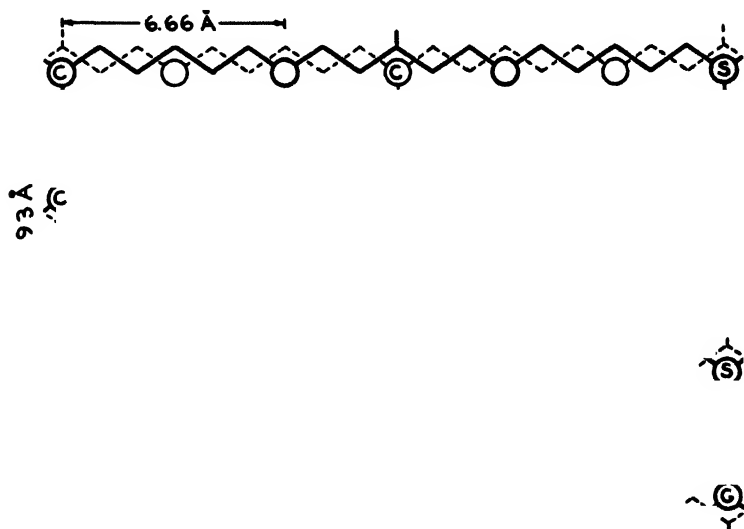
FIG. 10. Possible structure of β-keratin, showing the disposition of the zigzag chains in two adjacent layers, with the packing of R groups (circles) between them. A suggested distribution of cystine (C–C) and serine–glutamate (S–G) bridges is also indicated.

(figure 10). This is perhaps too speculative at this stage of the game, however; these details are not required by the present considerations.

α-KERATIN

When hair is stretched in steam, changing from α-keratin to β-keratin, there is an extension of the polypeptide chains of about 100 per cent, according to Astbury (13). If this is correct, the average length per residue in the direction of the fiber axis is about 1.7 Å. in the α-form. There is a strong x-ray reflection (or pair of reflections), due to planes approximately normal to this axis, spaced about 5.1 Å. apart,—about three times this average extension per residue. It seems necessary to assume, with Astbury, some sort of coiling of the chains.

Figures 11, 12, and 13 show three ways[5] in which a polypeptide chain can be coiled, consistent with the following assumptions:[6] (*1*) bond distances and angles are the expected ones; (*2*) atoms not directly bonded together are not too close together; (*3*) like atoms (or groups) are surrounded equivalently; (*4*) adjacent turns are connected by NHO hydrogen bridges. The structures of figures 11 and 12 have twofold screw axes of symmetry; there are two amino acid residues per coil; the identity distance, equal here to the distance between corresponding points in adjacent coils, is roughly 5 Å. The 5.1 Å. reflection can be accounted for on the basis of either of these structures, *provided one introduces the additional assumption that alternate R groups are much more potent x-ray scatterers*
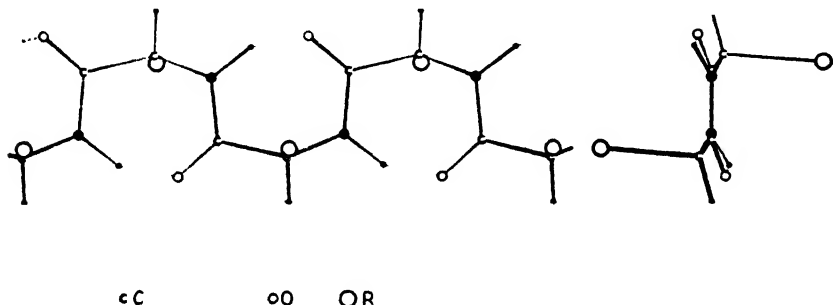

● C   o O   O R

FIG. 11. Two views of a hypothetical coiled structure for a polypeptide chain, with intrachain NHO hydrogen bridges.
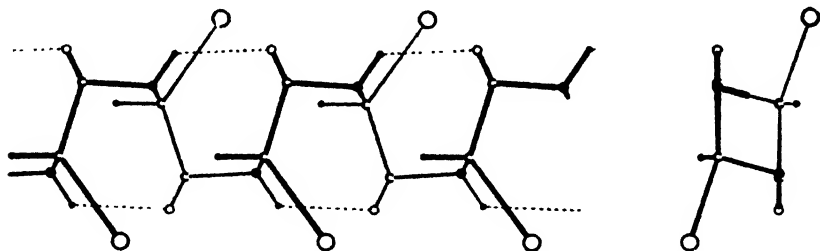

FIG. 12. Two views of a hypothetical spiral structure for a polypeptide chain, with intrachain NHO bridges.

than the intermediate ones. The change from α- to β-keratin, in either case, involves an extension of only about one-third, however, rather than the 100 per cent extension required by Astbury.

It might be possible, by distorting the bond angles considerably, to compress

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[5] These three structures were discussed, with slides and models, in a paper presented by the writer before the Division of Biological Chemistry at the Rochester Meeting of the American Chemical Society, September, 1937. The structure of figure 13 is apparently identical with one described in a recent paper by H. S. Taylor (55). The author is glad to express here his indebtedness to Professor Taylor for calling his attention to this paper.

[6] None of the models discussed for α-keratin by Astbury (7, 10, 13, 14, 29) is in agreement with these assumptions.

the model pictured in figure 12 until the distance per *three* residues in the direction of the spiral axis became 5.1 Å. This would give the 100 per cent α-to-β extension. To account for the 5.1 Å. x-ray reflection, one would then need to assume every *third* R group to be an especially strong x-ray scatterer.

In the structure depicted in figure 13 there are about three residues per turn of the spiral. The distance per residue (measured parallel to the spiral axis) is about 1.7 Å. This gives the 100 per cent extension in the α-to-β change, and also the 5.1 Å. x-ray spacing—provided every third R group is assumed to scatter x-rays much more strongly than the others.

It may be noted that there is nothing about this structure which requires exactly three residues per turn of the spiral. In fact, it would seem, from the models that have been made, that the bond distance and angle requirements are best satisfied by a slightly smaller number of residues per turn.

Still another hypothetical α-keratin structure will now be described. This may best be done by showing the relationship to the structure of figure 11. Figure 14a shows the ribbon-like structure of figure 11, slightly idealized for
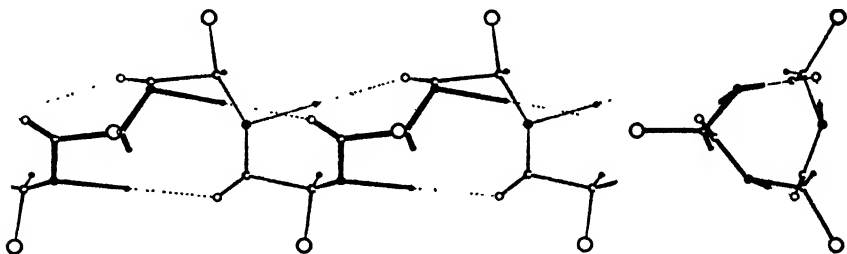

FIG. 13. Two views of another hypothetical spiral structure for a polypeptide chain, with intrachain NHO bridges.

simplicity; figure 14b is an edge-on view of this arrangement, showing the simple zigzag bending of the ribbon; figure 14c represents an alternative manner of bending, also possible without distortion of bond angles and distances from their preferred values. This arrangement gives the 100 per cent α-to-β extension and also accounts for the observed 5.1 Å. x-ray spacing—*without any additional assumptions regarding the scattering powers of the R groups.* At the present time, this type of structure seems to the writer more reasonable than any other of which he is aware.

It is worth pointing out that, if we assume β-keratin to have the structure of figures 3 and 10 and α-keratin to have that of figure 14 (a and c), the transition from β to α (or *vice versa*) involves no breaking of bonds (except the O···H bonds of the hydrogen bridges), either in cystine or other cross links or elsewhere, and no radical changes in bond distances or angles at any stage of the process. This statement is true whether the cross links connect chains within the same layer or in different layers.

The transition from β- to α-keratin can be visualized in the following way: The β-keratin structure can be readily warped in the manner indicated in fig-

ure 15, with no breaking of covalent bonds (either within the chains or in cross
links) or hydrogen bridges and with but little change in energy.   By a relatively
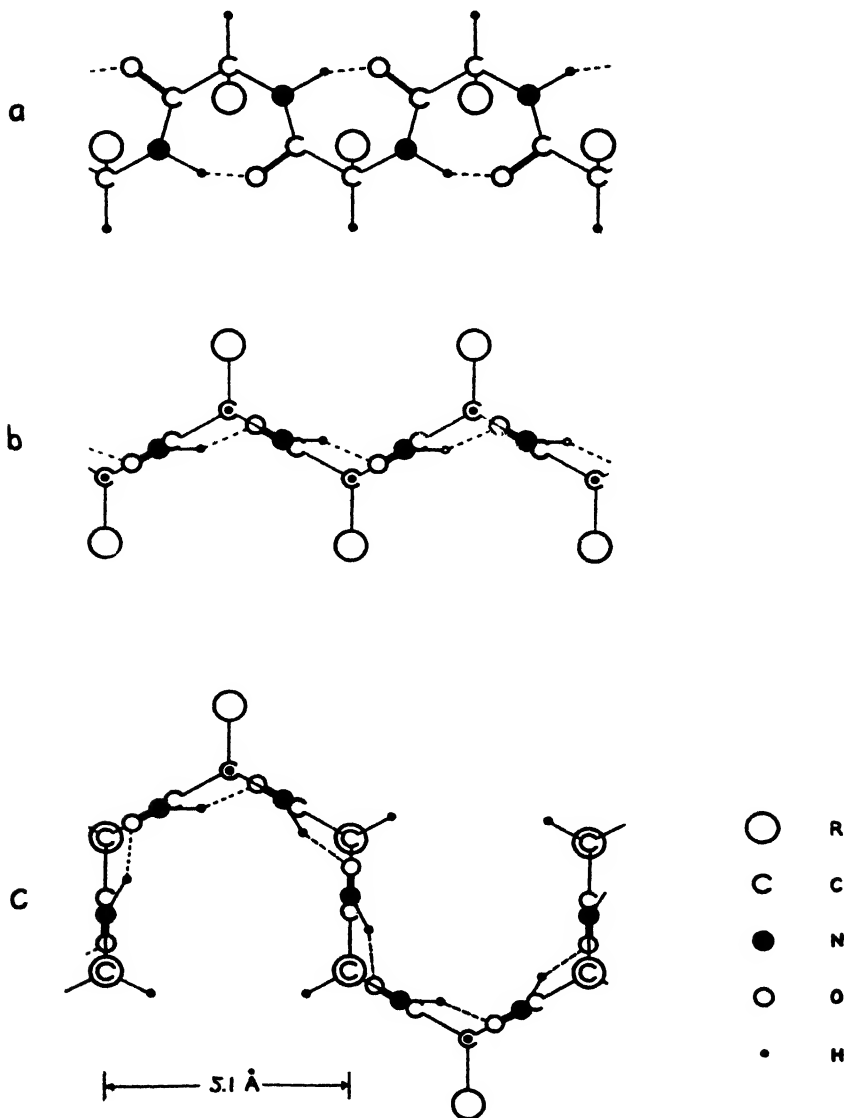

FIG. 14. (a) An idealized representation of the structure of figure 11; (b) an edge-on
view of this structure, showing the zigzag folding; (c) showing another manner of folding
the ribbon-like structure represented in 14a.

simple shift of position of each bridging hydrogen, the NHO bridges *between*
chains can now be replaced by similar bridges *within* the chains.   This gives the

distribution of atoms and bonds within each chain shown in figure 14a. The atoms shown in this figure, however, cannot be coplanar; the ribbon-like structure of the chain must be bent, at the carbon atoms of the CHR groups. Considering each chain by itself, we might expect this bending to take place in such a way as to give the structure of figure 11 and figure 14b. Since the x-ray and extensibility data seem to favor the figure 14c structure, we may infer that
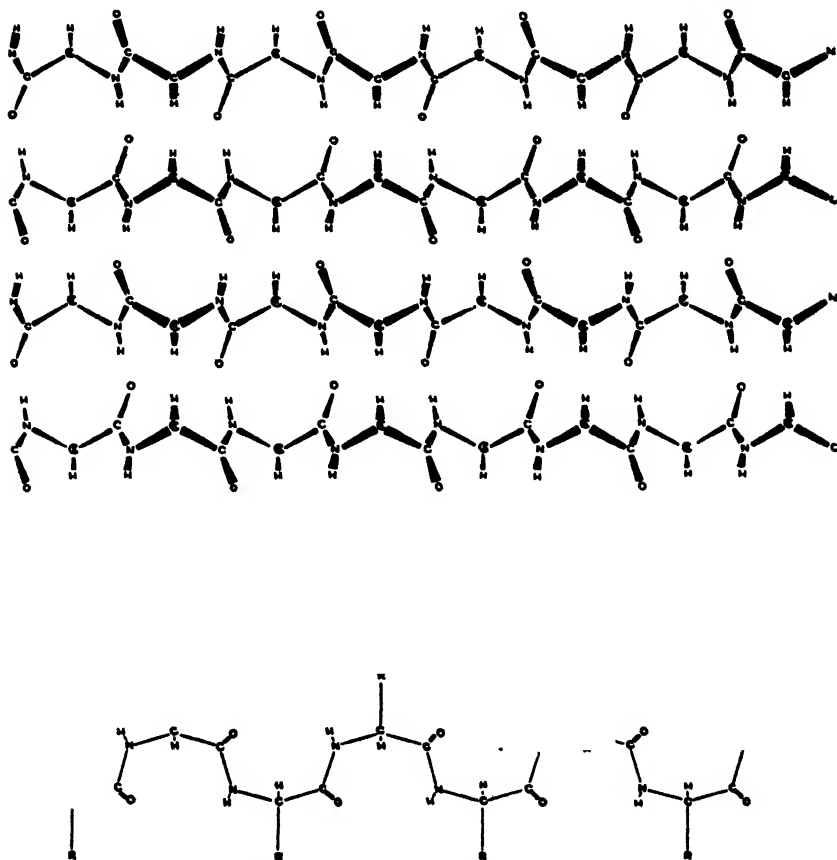
FIG. 15. Illustrating a possible intermediate stage between α-keratin and β-keratin.

the latter type of folding is more stable than the former—perhaps owing to a better distribution of R groups in the complete structure.

In addition to the strong 5.1 Å. "meridian" x-ray reflection already mentioned, α-keratin also gives two strong (though not well-defined) "equator" reflections, from sets of planes parallel to the fiber axis. One has a spacing of 27 ± 2 Å. The other is described by Astbury and Street (12) in the following words: "The most prominent interference on the equator is the disproportionately large spot formed round (001). There is little doubt that this is not a single reflection.

It is spread over about 3 Å. . . . The region of maximum density corresponds to
9.8 Å. . . . " This information, plus the small amount of additional informa-
tion available, is insufficient to enable one to deduce a single unique arrangement
of coiled chains—even assuming them to be of a particular type, say that repre-
sented in figures 14a and 14c. In one of several structures which look reason-
able, the chains are tied together in layers through cystine and serine–glutamate
bridges in the manner indicated in figure 16, these layers being stacked together
with an average interlayer distance of about 9 Å. The strong 27 Å. spacing
suggests that either the spacing between these layers is not uniform (every third
spacing being relatively small, perhaps), or else the compositions of successive
layers are not the same (every third layer having an excess of R groups which
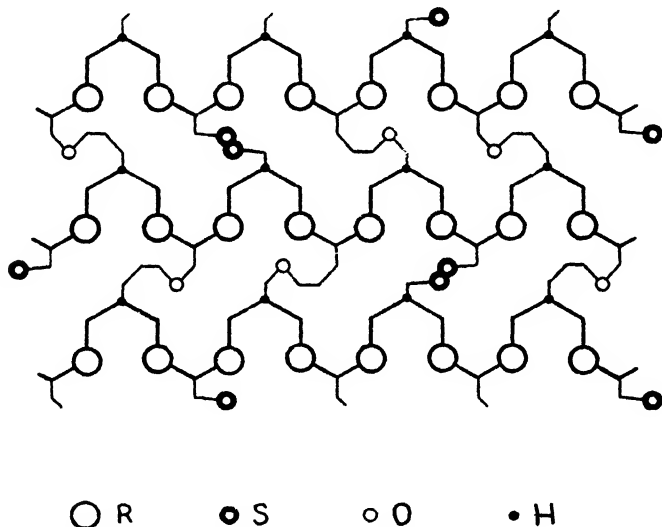
Fig. 16. Hypothetical distribution of spiral chains of the type of figure 14 (a and c) in a
layer of the α-keratin structure, assuming cystine and serine–glutamate bridges connecting
the chains.

are especially strong x-ray scatterers, for example), or both. A strong third
order (9 Å.) spacing would be expected; it may well be present, being included
in the strong, very diffuse spot described above.

In addition to the few strong diffuse reflections discussed above, certain sub-
stances (e.g., sea gull's quill and porcupine quill) classed by Astbury as α-keratin
show also a considerable number of other reflections, some corresponding to
quite large (up to 100 Å.) interplanar distances. These reflections may be at-
tributed to the distribution of R groups in the structure; the true unit of struc-
ture must be much larger than the pseudo unit of the idealized pattern just
described. Astbury (9) interprets MacArthur's (9) "meridian" reflections from
porcupine quill as indicating a probable identity distance in the direction of the
fiber axis of 658 Å. Pending the publication of more complete data, however,
further discussion of the possible significance of these results seems unwarranted.

COLLAGEN

Figure 17 shows a way in which polypeptide chains can be coiled spirally so as to give NHO bridges *between* different chains, holding them together in layers. (The structures represented by figures 6 and 7 are not layer structures.) The R groups extending above or below each layer are very uniformly distributed, without crowding. The layers can be piled together in such a way (figure 18) as to give approximately a "close-packed" arrangement of R groups between each pair.
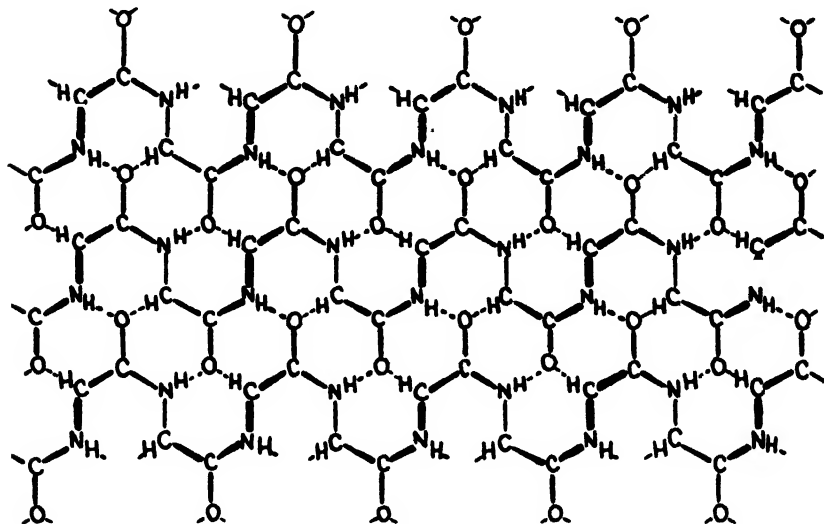
FIG. 17. Hypothetical structure of a layer of spiral polypeptide chains in collagen. An R group (or H atom, in case the residue in question is glycine) is assumed to be directly over or directly under the C of each CH.

The pseudo unit of the structure represented in these figures (on the assumption that all R groups are equivalent) has the following dimensions:

$$a \sim 4.5 \text{ Å}.; b \sim 5.8 \text{ Å}.; c \sim 22 \text{ Å}.; \beta \sim 90°$$

(The c distance, assumed to be twice the average distance between the median planes of adjacent layers, varies greatly with the water content.)

This structure seems a reasonable one for collagen. It accounts simply for the observed (7, 10, 26, 59) strong 2.9 Å. x-ray reflection from planes nearly normal to the fiber axis and the strong equator reflections corresponding to distances of about 4.4, 5.4, and 11 Å. The indices of these four reflections, on the basis of the pseudo unit, are 022, 101, 004, and 002, respectively. In spite of this, however, it must be emphasized that this structure must be considered only as a guess. It is certainly neither deducible from the x-ray observations nor proven correct by them.

Because of the differences in the R groups, the true unit must be much larger than the pseudo unit just described. The observed large-spacing reflections

from planes parallel to the fiber axis may be considered as evidence for this. The long-spacing reflections from planes normal to the fiber axis, such as the many orders of a 640 Å. spacing reported by Bear (16), are doubtless the result of the banded structure (of the same periodicity) which collagen fibers possess, according to electron-microscope studies of Schmitt, Hall, and Jakus (53). Dense regions, which might possibly have a structure of the type of figure 17, alternate with relatively transparent regions having a much more open structure.

The analytical data (7, 10, 17, 18, 20, 27, 38) on collagen suggest that one-third of the residues in collagen are glycine, one-sixth are proline, one-ninth are hydroxyproline, one-ninth are alanine, etc. (see table 3). The large fraction of residues which are proline or hydroxyproline, in which the carbon atom of the
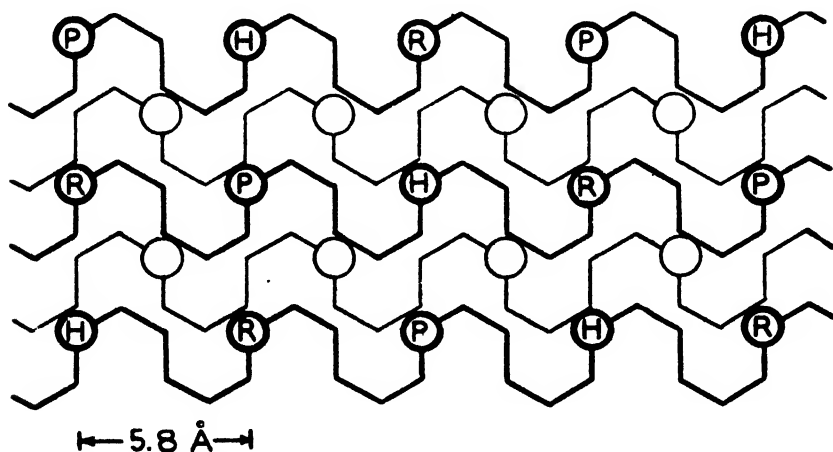
Fig. 18. Possible manner of packing adjacent layers of the type of figure 17. Heavy circles containing the letters P, H, and R denote R groups (or H atoms) pointing *up* from the lower layer; light circles, without letters, denote R groups (or H) pointing *down* from the upper layer. The letters P, H, and R indicate a suggested distribution of proline (and oxyproline), glycine, and other residues, respectively, on the assumption that these three classes are present in equal numbers.

CHR and the adjacent nitrogen atom in the polypeptide chain are both part of a five-membered ring, is probably important. Assuming, as usual, a levo-configuration around this carbon atom, the orientation of the ring relative to the neighboring bonds in the chain is fixed. Residues of this sort cannot fit into any of the structures discussed above for silk, α-keratin, or β-keratin, but they do fit readily into a structure of the type of figure 17. The ring extends either above or below the layer, without any crowding. This may explain why collagen assumes this type of structure. It seems equally reasonable to assume, however, that the collagen structure is, in general, the stable one, the α-keratin structure being adopted only when there are sufficient cystine or other bridges between adjacent chains.

In figure 17, C—H···O hydrogen bridges, connecting the CHR groups

with CO groups, have been indicated. Although CHO bridges are not common, they would be expected in a structure of this type, being stabilized by resonance and by synchronized oscillations of neighboring bridges. One out of several modes of resonance contributing to the stability of the structure can be represented by the formulation
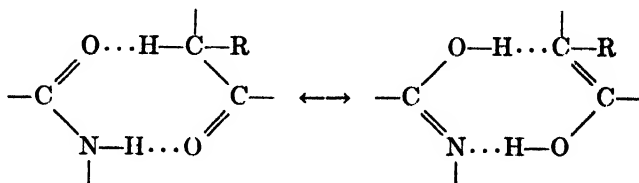
Wherever one of the R groups is proline or oxyproline, the adjacent nitrogen atom in the chain (which is also a part of the proline ring) has no hydrogen atom directly attached to it; therefore, it cannot form a hydrogen bridge to the nearby carbonyl oxygen. In view of the neighboring CHO bridges, however, the absence of the NHO bridge would not be expected to cause a rupture or great distortion of the structure pattern.

CONCLUSION

No claim can be made that the structures proposed here for silk fibroin, keratin, and collagen are proven, that they are correct in all their details, or that they are complete. The writer does claim, however, that they are in considerably better agreement with the available experimental data than are the other structures which have been proposed. Further analytical and x-ray data, he feels sure, will either verify these structures or will show that others quite closely related to them are correct; they should also lead to further refinements, especially as regards the distribution of R groups.

In this paper no reference has been made to the structures of globular proteins. There is every reason to believe, however, that the same principles apply as in the case of the fibrous proteins.

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˙ LIQUID AMMONIA RESEARCH—1942

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CONTENTS

I. INTRODUCTION

This, the tenth paper in a series (11, 13, 57, 58, 59, 61, 64, 65, 67) initiated in 1933, is concerned primarily with researches described by American workers. With very few exceptions, information relating to publications which have appeared in foreign periodicals is essentially that which has been made available through the various abstracting services. Including patents, the number of publications which have appeared or have become available during the past year is approximately one-half the average number for the preceding nine years.

II. PHYSICOCHEMICAL STUDIES

Methods have been described for the investigation of the effects of inorganic electrolytes (45) and certain organic compounds (46) upon the electrocapillary curves of mercury in liquid ammonia at or near room temperature. In the application of these methods to the study of inorganic electrolytes, ammonium nitrate was employed as the stock electrolyte and solutions containing sodium chloride, sodium bromide, or potassium iodide were prepared and investigated. Liquid ammonia solutions of these electrolytes were found to shift the maximum in the electrocapillary curve in a manner comparable to, but to a degree greater than, that observed previously for the corresponding aqueous solutions. Calculation of the capacity of the electric double layer resulted in a value of 11 μF per square centimeter, which is considerably lower than the value of 17 to 18 μF per square centimeter found when water was used. It has been suggested that this result may be due to the lower dielectric constant of liquid ammonia. Although liquid ammonia solutions of ammonium nitrate containing toluene, xylene, mesitylene, ethylbenzene, propylbenzene, cyclohexane, naphthalene, or tetralin resulted in a decrease in interfacial tension, these solutions failed to produce any shift in the maximum of the electrocapillary curve. With increase in length of the side chain, adsorption on the surface of the mercury was found to increase.

Audrieth and coworkers (2) have provided comparative data relative to the catalytic influence of salts upon ammonolytic and aminolytic reactions of esters and have suggested that the effects heretofore designated as acid catalysis in basic solvents may be only a special case of a more general type of electrolyte catalysis. A related but independent investigation (36) has shown that catalytic effects of this type observed in connection with the ammonolysis of both esters and organic halogen compounds are accompanied by increases in energy of activation. These and subsequent studies (70) provide quantitative proof of the assumption that these effects should be classified as electrolyte catalysis rather than acid catalysis.

Using a differential manometer and a method permitting rapid and exact equalization of temperature in the two liquids, Kirshenbaum and Urey (31) have redetermined the vapor pressure differences of the isotopic ammonias, NH_3 and ND_3. The results of their measurements have been found to be represented accurately by the expression

$$\log_{10} P_{NH_3}/P_{ND_3} = (46.25/T) - 0.14003$$

The triple point for ammonia (195.68°K.) was found to be in excellent agreement with the value reported by Overstreet and Giauque (60); however, that found for 98 per cent trideuterio-ammonia (198.79°K.) was lower than the value reported previously by de Bruyne and Smyth (16). Jaffe (29) has pointed out that the color of the light reflected from a saturated solution of lithium in liquid ammonia [which contains $Li(NH_3)_4$] is dependent upon the angle of incidence. Measurement of the Hall effect showed that the saturated solution contains one mobile electron for each atom of lithium and, in terms of this electron density, the observed color can be explained satisfactorily by the classical theory of dispersion of electrons. Procedures for the electroplating of gold from liquid ammonia solutions of gold salts have been described by Kushner (34).

III. INORGANIC REACTIONS

The preparation of bright red (and apparently amorphous) potassium cyanonickelite, $K_2Ni(CN)_3$, in a pure condition has been accomplished by Eastes and Burgess (18) by the interaction of potassium and an excess of potassium cyanonickelate, $K_2Ni(CN)_4$, in liquid ammonia at its boiling point. This product, which had not been isolated previously, was also produced by reactions effected in aqueous solutions. When the reduction of potassium cyanonickelate was effected in liquid ammonia, using an excess of potassium, there was obtained a yellow solid product having a composition represented by the formula $K_4Ni(CN)_4$. These reduction products of the nickelate are of particular interest in that $K_3Ni(CN)_4$ is presumably a compound of univalent nickel, while $K_4Ni(CN)_4$ may perhaps be looked upon as a compound involving zerovalent nickel. Analogous reactions have been observed when potassium cyanonickelate was reduced by liquid ammonia solutions of calcium (19). On the other hand, the complex cyanides $KAg(CN)_2$, $K_2Cd(CN)_4$, and $K_3Cu(CN)_4$ were reduced by liquid ammonia solutions of potassium to the pyrophoric elemental metals. For

reasons not indicated, potassium cyanozincate, $K_2Zn(CN)_4$, was reduced by sodium rather than by potassium and in this case a non-pyrophoric precipitate of elemental zinc was obtained.

A study of reactions of certain oxides of cobalt and iron in liquid ammonia (44) has shown that, at room temperature, cobalt(III), cobalt(II), and iron(II) oxides are insoluble in and unreactive toward liquid ammonia. Cobalt(III) oxide was not attacked by liquid ammonia solutions of ammonium chloride or ammonium nitrate at 100°C., while, under the same conditions, the oxides of divalent cobalt and iron were partially dissolved and in these cases the extent of reaction was found to be the more pronounced in the case of ammonium chloride solutions. The action of liquid ammonia solutions of potassium amide at room temperature upon these o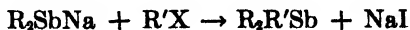xides was found to result in the formation of complex mixtures of soluble and insoluble products, of which only elemental cobalt could be separated and identified. By reaction with liquid ammonia solutions of potassium at 0°C., cobalt(III) oxide was reduced first to cobalt(II) oxide and finally to elemental cobalt to an extent dependent upon the quantity of potassium employed in reaction with a given weight of oxide. Under similar conditions, iron(II) oxide was reduced only to a limited extent which was largely independent of the quantity of potassium employed. The comparative behavior of cobalt(III) and iron(II) oxides indicated that the reduction products of the former are much less effective catalysts for the conversion of potassium to potassium amide than is the elemental iron formed by the reduction of iron(II) oxide.

The addition of liquid ammonia to concentrated solutions of ammonium sulfate (formed by the interaction of gypsum and ammonium carbonate) has been suggested as a means of effecting precipitation in a manufacturing process which provides ammonium sulfate of 75 per cent purity (14).

A series of unsymmetrical organoantimony compounds (72) has been prepared in liquid ammonia by the reduction of disubstituted antimony(III) iodides,

$$R_2SbI + 2Na \rightarrow R_2SbNa + NaI$$
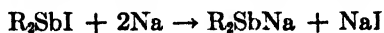
followed by reaction of the resulting sodium salt with an appropriate organic halide,

$$R_2SbNa + R'X \rightarrow R_2R'Sb + NaI$$

Methods for the preparation of unsymmetrical organolead compounds have been described by Apperson (1) and Bindschadler (6). These compounds were studied in relation to their ease of cleavage by alkali metals, which was found to result in the formation of unsymmetrical organolead–sodium compounds. In the course of this investigation, one organolead compound containing divalent lead, $(C_2H_5)_2Pb$, was prepared. The order of decreasing ease of cleavage of the substituent groups was found to be allyl, benzyl, sec-butyl, butyl, ethyl, methyl, and phenyl. In connection with a general discussion of the chemistry of organobismuth compounds, Gilman and Yale (23) have called attention to the utility of liquid ammonia as a medium for the formation of salts of the type R_2BiM or
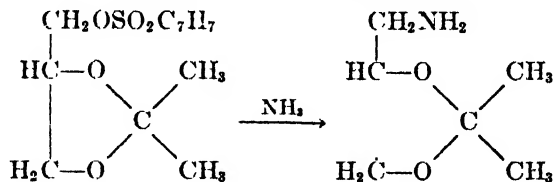
$(R_2Bi)_2M$ and their subsequent use in the preparation of unsymmetrical organobismuth compounds and of water-soluble organobismuth compounds of potential therapeutic value.

IV. ORGANIC REACTIONS

A. Ammonolysis

An extended study of the interaction of benzil and liquid ammonia or liquid ammonia solutions of potassium amide or ammonium chloride has provided information with regard to the identity and yields of the various products, together with methods for the separation and estimation of these products (37). Reaction with liquid ammonia at 35°C. was found to yield benzamide, 2,4,5-triphenyloxazole, "imabenzil," "benzilimide," and traces of tetraphenylpyrazine. The constitution of imabenzil and of benzilimide has not been definitely established. Addition of potassium amide resulted in an increase in the yield of benzamide, a decrease in the yield of imabenzil, and elimination of 2,4,5-triphenyloxazole from among the reaction products. At 103°C., benzamide, 2,4,5-triphenylglyoxaline ("lophine"), 2,4,5-triphenyloxazole, and small quantities of tetraphenylpyrazine were produced by the reaction between benzil and liquid ammonia, while in the presence of potassium amide the yield of benzamide was increased, that of lophine was decreased, and no 2,4,5-triphenyloxazole was obtained. The influence of ammonium chloride was not pronounced at either temperature.

In connection with the study of the preparation of l-glycidol from $d(+)$-acetoneglycerol, Sowden and Fischer (55) have shown that α-(p-toluenesulfonyl)-d-acetoneglycerol is ammonolyzed to l-1-aminoacetone-2,3-propanediol.

$$
\begin{array}{ccc}
\mathrm{CH_2OSO_2C_7H_7} & & \mathrm{CH_2NH_2} \\
| & & | \\
\mathrm{HC-O}\diagdown\quad\diagup\mathrm{CH_3} & \xrightarrow{\ \mathrm{NH_3}\ } & \mathrm{HC-O}\diagdown\quad\diagup\mathrm{CH_3} \\
| \qquad\quad \mathrm{C} & & \qquad\quad \mathrm{C} \\
\mathrm{H_2C-O}\diagup\quad\diagdown\mathrm{CH_3} & & \mathrm{H_2C-O}\diagup\quad\diagdown\mathrm{CH_3}
\end{array}
$$

The ammonolysis was carried out by allowing the p-toluenesulfonyl derivative to react with anhydrous liquid ammonia at room temperature over a period of 98 hr.

B. Reactions of alkali amides

White and Bergstrom (68) have reported that 2-phenylquinoline-4-carbonamide reacts with potassium amide in liquid ammonia at room temperature to form 4-amino-2-phenylquinoline in approximately 45 per cent yield. If potassium nitrate is present during the reaction, the yield is almost quantitative. Only certain homologs of the above carbonamide reacted similarly to yield amines: o-benzoylbenzamide yielded small quantities of o-aminobenzophenone, while the other amides studied did not react. Since it is believed improbable that the —CONH$_2$ group is replaced directly by —NH$_2$, it has been suggested

that potassium amide reacts with $RCONH_2$ reversibly to form the ion $RCON^{--}$, which loses two electrons to potassium nitrate to form RNCO by rearrangement. The excess potassium amide converts this product to RNHK. The over-all reaction may be represented by the equation

$$RCONH_2 + 3KNH_2 + KNO_3 \rightarrow RNHK + KNCO + 2NH_3 + KOH + KNO_2$$

Experiments conducted with isocyanates support the foregoing mechanism. 9-Amino-9-phenylfluorene was found to react with potassium amide and potassium nitrate to form 9-aminophenanthridine, the expected 9-phenylphenanthridine being converted to the 9-amino compound. Under similar conditions triphenylmethylamine yields benzamide, and in this reaction it is believed that benzophenone anil is first formed by rearrangement and subsequently cleaved by potassium amide to form benzamidine which, in turn, is hydrolyzed to benzamide.

An excess of potassium amide or sodium amide in liquid ammonia at $-33°C$. or at room temperature has been found to react with nitrobenzene to form a deep reddish brown solution from which a dark-colored precipitate separates slowly (4). At the same time, gaseous nitrogen is liberated in the approximate ratio of 0.5 mole per mole of nitrobenzene. Several other nitro compounds have been shown to react in a similar manner. Sodium amide or potassium amide in excess was found to react with nitrobenzene and 2-naphthol in liquid ammonia to form 1-phenylazo-2-naphthol in yields up to 30 per cent. Since it was shown that sodium benzeneisodiazotate does not react with 2-naphthol in the presence of sodium amide, the normal diazotate ($C_6H_5N=NONa$) is probably the intermediate in the reaction. The following partial mechanism has been suggested:

$$C_6H_5N\overset{O}{\underset{O}{\diagup}} + NaNH_2 \rightarrow C_6H_5\overset{O}{\underset{ONa}{N}}NH_2 .$$

$$C_6H_5\overset{O}{\underset{ONa}{N}}NH_2 + NaNH_2 \rightarrow C_6H_5N=NONa + NaOH + NH_3$$
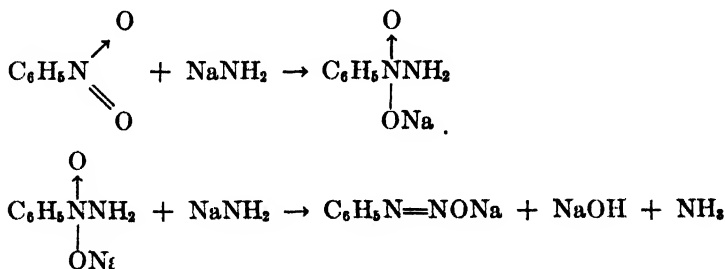
Bergstrom and coworkers (5) have also shown that sodium, potassium, or barium diphenylamide (prepared by the action of the appropriate metal amide on diphenylamine in liquid ammonia) reacts with nitrobenzene to form p-nitrotriphenylamine in yields up to 45 per cent. The reaction may be carried out at $-33°C$. or at room temperature, using liquid ammonia or absolute ethyl ether as the solvent. o-Nitrotoluene was found to react with sodium diphenylamide in liquid ammonia at $-33°C$. to form 2,2'-dinitrobibenzyl in 36 per cent yield, while only small quantities of 4,4'-dinitrobibenzyl were obtained when p-nitrotoluene was employed under similar conditions.

A group of diethyl α-(alkoxyethyl)alkylmalonates, [CH₃CH(OR)CR'-(CO₂C₂H₅)₂], have been prepared by the reaction of α-chloroethyl alkyl ethers with the sodium salts of diethyl alkylmalonates in benzene–ether solution. The sodium salts were prepared by adding the alkylmalonic esters to liquid ammonia solutions of sodium amide at temperatures below the boiling point of ammonia (41). The use of liquid ammonia as a medium for the amination of heterocyclic bases by alkali amides has been discussed in considerable detail by Leffler (35). Applications involving the use of ammonia as the reaction medium are based almost entirely upon the investigations of Bergstrom and his coworkers (62).

C. *Reactions of solutions of metals*

Freudenberg and coworkers (22) have made an extensive investigation of the action of liquid ammonia solutions of potassium at room temperature upon sprucewood meal, beechwood meal, and spruce lignin. In order to obtain comparative data useful in the interpretation of the observations recorded, they have also studied the reactions of ammonia solutions of potassium upon a number of "model substances" including phenol ethers, glucosides, coumarone, coumaran, and chroman derivatives. Treatment of sprucewood meal with a solution of potassium over a period of several hours resulted in degradation to a small ammonia-soluble fraction (which consisted of phenolic decomposition products of lignin) and an ammonia-insoluble portion. The latter was separated into a methanol-insoluble fraction (which was subsequently divided into carbohydrate and lignin fractions) and a methanol-soluble fraction containing most of the lignin present in the original sample of wood. This lignin was found to have a relatively high —OH content, which is attributed to the cleavage of phenolic ethers with resultant formation of new —OH groups. In the case of beechwood meal, a somewhat more complicated reaction produced a larger ammonia-soluble fraction and the size of the other fractions was found to vary considerably with the concentration of potassium employed. Treatment of cuproxam lignin with potassium in ammonia converted all of the lignin to forms soluble in either liquid ammonia or methanol. The interpretation of these and other similar observations has been based largely on the over-all behavior of the model substances toward solutions of potassium rather than on any detailed study of the reactions of each of these substances.

A study of the reduction of benzoxazole and benzothiazole (32) has shown that their reactions with liquid ammonia solutions of sodium at −33.5°C. result in the rupture of the heterocyclic rings and formation of sodium salts as the primary reduction products. These salts were converted to the corresponding Schiff bases by treatment with ammonium bromide or ethyl bromide or to the aminophenols or thiophenols by hydrolysis of the sodium salts (or the Schiff bases). More extensive reduction at the same temperature was effected by reducing liquid ammonia solutions of the oxazole or thiazole by the hydrogen generated by the interaction of sodium and ammonium bromide. Thus, benzoxazole was reduced by hydrogen to o-(methylamino)phenol. In connection with this work, limited information relative to the reduction of 2-phenylbenzoxazole and 2-chlorobenzothiazole has also been recorded.

Greenlee and Fernelius (24) have suggested that the formation of pure *trans*-olefins by treatment of dialkylacetylenes with sodium in liquid ammonia proceeds through a mechanism in which the *trans* configuration is established by electrostatic repulsion. An analogy between this mechanism and the Walden inversion is suggested. Hennion and Murray (25) have described certain catalytic addition reactions of acetylenic alcohols which were prepared, as described previously (63), by the condensation of the appropriate aldehyde or ketone with sodium acetylide in liquid ammonia.

Certain dextrins isolated from corn sirup have been methylated completely by sodium and methyl iodide, using liquid ammonia as the reaction medium (39). This now rather generally well known method was found to yield better results than other methods which were tried. Similarly, the dextran obtained from sucrose by the action of *L. mesenteroides* has been methylated completely, i.e., to a methoxyl content of 45.6 per cent (38). Liquid ammonia may be used as a medium for the introduction or removal of alkyl or other substituent groups. The methyl group of *dl*-methionine may be removed by treatment in liquid ammonia with the calculated quantity of sodium (56). If this treatment is followed by addition of benzyl chloride, *S*-benzyl-*dl*-homocysteine is obtained. This series of reactions is the reverse of that employed by du Vigneaud and Patterson (12) for the preparation of methionine from homocysteine. If an excess of sodium is employed in the reduction of *dl*-methionine, followed by addition of benzyl chloride, *N*-dibenzyl-*S*-benzyl-*dl*-homocysteine is formed.

The liquid ammonia–sodium method for the analysis of organic substances for halogens has been used in the determination of chlorine, bromine, and iodine in a series of *p-s*-alkylhalobenzenes (26).

D. Other organic reactions

In a study of evidence bearing upon the structure of salts of hydroxyanthraquinones, Scholl and coworkers (54) have prepared a considerable number of ammonium salts by the interaction of the various hydroxyanthraquinones and liquid ammonia. It has been shown that these salts are predominantly ionic, and particular attention has been directed toward the relationship between the colors of these (and other) salts and the electronic structures of the corresponding anions.

A series of ferrihemochromogens has been prepared by dissolving crystalline or amorphous insulin in anhydrous liquid ammonia, followed by treatment of the resulting solutions with varying amounts of ferriheme chloride (3). Insulin was found to combine with ferriheme up to a maximum ratio of 1:8, indicating a relationship of one insulin nitrogen to one ferriheme iron atom. The physiological activity of this conjugate proved to be no different from that of ordinary insulin. When commercial curare is added to liquid ammonia, more than one-half of the total amount passes into solution as inert material, leaving the active principles undissolved (53). If the ammonia-insoluble fraction is treated with an equal weight of glycine, it becomes more potent, prolonged in its action, and less toxic than curare. In connection with studies relating to the establishment of the structure of biotin, du Vigneaud and coworkers (17) have converted

ethyl ζ,η-dioximinopelargonate to ethyl ζ,η-diaminopelargonate by hydrogenation over Raney nickel in a solvent medium consisting of liquid ammonia containing a small quantity of methanol.

$$CH_3C(=NOH)C(=NOH)(CH_2)_5COOC_2H_5 \rightarrow$$
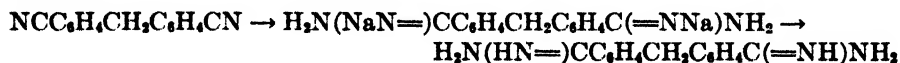$$CH_3CH(NH_2)CH(NH_2)(CH_2)_5COOC_2H_5$$
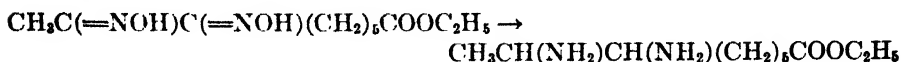
In an attempt to produce plastics from inexpensive domestic materials, Roberts (51) has prepared plastic elastomers by treatment of proteins such as casein or gluten and rubber latex with liquid ammonia. Removal of the ammonia was found to leave plastics having the desirable properties of toughness, resiliency, and hardness. The structure or mode of formation of these products is not known.

V. PATENTS

Previous papers in this series have called attention to numerous patents relating to processes for the large-scale production of melamine. More recent patents issued describe improvements in the design of equipment suited to the production of melamine from liquid ammonia and cyanamide or dicyanamide (71), conditions of temperature and concentration favorable to the formation of melamine from liquid ammonia and dicyanodiamide (69), and a method for the production of liquid ammonia solutions of cyanamide (15) suitable for use in the production of melamine. In this latter process cyanamide is produced, for example, by the interaction of calcium cyanamide and ammonium carbonate in the presence of liquid ammonia which serves as a solvent for the liberated cyanamide.

In addition to those indicated above, a number of recently issued patents have been concerned with the use of liquid ammonia in the production of other organic nitrogen compounds. Hill (27) has described the details of a process for the liberation of aliphatic bases such as guanylurea from their salts (e.g., the sulfates) by treatment with liquid ammonia or alkali metal amides in the presence of ammonia. By the selective hydrogenation of acyclic dinitriles in liquid ammonia and in the presence of a nickel catalyst, Rigby (49) has developed a process for the preparation of acyclic monoaminonitriles, such as ω-aminocaprinitrile. Improved yields resulting from a more selective control over extent of hydrogenation have been realized through the use of cobalt-containing catalysts having relatively mild catalytic activity (50). On the other hand, dinitriles have been converted to the corresponding diamidines (20) by reaction with sodium amide in liquid ammonia. This conversion may be indicated as follows:

$$NCC_6H_4CH_2C_6H_4CN \rightarrow H_2N(NaN=)CC_6H_4CH_2C_6H_4C(=NNa)NH_2 \rightarrow$$
$$H_2N(HN=)CC_6H_4CH_2C_6H_4C(=NH)NH_2$$

The use of liquid ammonia as a reaction medium is claimed but is not illustrated in the description of a patented process for the production of unsaturated amines of the acetylene series by the interaction of ammonia and acetylene in the presence of heavy-metal catalysts which are capable of forming acetylides, e.g.,

copper, silver, and mercury (48). Addition compounds of epinephrine and glycine, or glutamic acid, dextrose, ascorbic acid, lactic acid, cholesterol, urea, gelatin, etc., have been produced by bringing the two reactants together in liquid ammonia at $-33.5°C$. under anhydrous conditions (52). The conjugates so obtained have been found to produce an increase in blood pressure of greater duration than may be obtained through the use of epinephrine or epinephrine hydrochloride.

Patented processes for the production of non-nitrogenous organic substances include a method for the preparation of substituted ethynylcarbinols of high molecular weight (8). Ketones such as myristone, laurone, stearone, p-biphenylyl heptadecyl ketone, etc. are condensed with an alkali metal acetylide (or substituted acetylide) in liquid ammonia and the resulting alkali metal salts are hydrolyzed to afford the corresponding ethynylcarbinols. Condensation products of allyl or substituted allyl halides (30) have also been produced by condensing, for example, allyl chloride with itself or its derivatives by treatment with liquid ammonia solutions of alkali or alkaline-earth metals. Additional patents have been issued in connection with the use of liquid ammonia as a medium for the formation of alkaline-earth metal salts of cellulose from carbohydrate materials such as cotton or wood pulp and the utilization of these salts (or the alkali metal salts) in the production of cellulose acetate (43). Salts formed similarly from partially substituted cellulose may be used in the formation of more highly substituted products, e.g., diethylpropylcellulose from the reaction between diethylcellulose and sodium in liquid ammonia, followed by interaction of the resulting sodium salt and propyl bromide (7).

A process for the separation of carboxylic acids from polybasic inorganic acids (28) has been based upon the fact that, upon treatment with liquid ammonia, the carboxylic acids form soluble ammonium salts. The salts of the organic acids are recovered by filtration, followed by evaporation of the solvent ammonia. Muskat and Ayers (47) have developed a method for the purification of sodium hydroxide through the removal of silica by treating concentrated caustic solutions with a quantity of liquid ammonia sufficient to precipitate most of the silica present but insufficient to cause separation of two liquid phases, while maintaining the temperature at a level such that separation of solid sodium hydroxide does not occur. Liquid ammonia has also been used as a medium for the incorporation of sensitizers into chlorate or perchlorate explosives (9). Provision has been made for the synthesis of ammonia by bringing together the constituent gases in a liquid medium, which may consist of liquid ammonia, in which a suitable catalyst is dispersed, immersed, or dissolved (40). Other recent patents involving the use of liquid ammonia are concerned with the production of sulfonamides (e.g., by the interaction of paraffin wax sulfonyl chloride and liquid ammonia) suitable for use in the compounding of lubricants (10) and with the removal of asphaltic materials from lubricating oils (42). In the latter process, the oil is treated with liquid propane together with a quantity of liquid ammonia sufficient to permit precipitation of a substantial quantity of non-paraffinic constituents.

VI. GENERAL

Accounts of experiments on the use of liquid ammonia solutions of acetylene as a motor fuel (21, 33, 66) indicate that a solution containing 22 per cent of acetylene provides a fuel having a high octane number and providing an ammonia-free exhaust. Danger of explosion arises only if the liquid phase contains 30 per cent by weight (or more) of acetylene, while gaseous mixtures of acetylene, ammonia, and air must contain at least 15 per cent of acetylene if complete combustion of the acetylene is to be realized. The fuel is prepared by passing gaseous acetylene into tank cars of liquid ammonia and, during use, the fuel is carried in light alloy-steel tanks which are not subject to corrosion by the acetylene-ammonia mixture. In connection with the study of the flammability of this gasoline substitute, the vapor pressures of the system acetylene-ammonia have been studied at −33°, 0°, 25°, and 40°C. as a function of the composition of both the gaseous and the liquid phases.

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RADIOACTIVE ISOTOPES FOR THE STUDY OF TRACE ELEMENTS IN LIVING ORGANISMS[1]

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Radioactive trace elements are grouped according to certain selected characteristics and listed in tables. Indirect tracers are discussed in addition to the trace element itself. Two illustrative trace element experiments are detailed for the purpose of more clearly describing the Geiger–Müller counter technique of measurements of artificial radioactivity.

I. INTRODUCTION

The authors are pleased to have had the opportunity to contribute to the Symposium on Trace Elements, not only for the honor involved but also because it was a very helpful stimulus to their revision of the relative value of the radioactive isotopes as tracers on the basis of recent work in nuclear physics.

It is gratifying to present a critical analysis of artificial radioactivity in its primary significance, that is, in the service of mankind. We all remember the exciting time at the end of 1936 when Lawrence (19) disclosed that he had produced radioactive sodium in the cyclotron in an amount equivalent to 200 mg. of radium in its gamma radiation. This introduced a new era, signified by the fact that not only could thousands of dollars worth of radioactive matter of intensity comparable to that of radium be produced artificially and in a short time, but also by the fact that all chemical elements could be made radioactive and, as a result, all elements in living organisms could be traced by their corresponding radioactive isotopes.

However, the expectation of a simple solution of many important problems by means of artificial radioactivity soon was doomed to disappointment in many cases.

It was found early that radioactive isotopes could not be used as tracers for many of the most important elements in living organisms because they disintegrated so rapidly that it was impossible to trace the labeled elements or they disintegrated too slowly, emitting radiation of insufficient intensity for detection or, even if the half-life were favorable, weak radiation excluded easy experimental procedure.

After five years of the most extensive research in nuclear physics, the general picture can be presented as follows: (*1*) Many new isotopes of the most important elements, with sufficiently long life and high intensity of radiation, have been found. (*2*) The technique of measurement of radiation, developed to a

very high degree, permits the application of tracers even with weak radiation. (3) The study of a number of elements still can not be benefited by the application of radioactive tracers, because of the lack of suitable isotopes.

A present trend in biology and related fields is to evaluate the significance and the effect in the living organism of elements present in traces. Some of these trace elements are necessary and therefore always present in living organisms, while others occur occasionally and may even be toxic. In this paper radioactive isotopes corresponding to both groups are presented, but their classification is based on their relative merits as tracers and not on the biological effects of the element traced.

The best yields of different radioactive isotopes are secured today by bombarding various elements in a cyclotron with high-velocity particles such as heavy hydrogen, ordinary hydrogen, helium, and neutrons, or, as more correctly expressed, they are obtained by means of different nuclear reactions[2].

An important criterion in the classification of nuclear reactions, for the production of radioactive isotopes to be used as tracers, is the atomic number of the active isotope formed. Is it the same as that of the element taken for activation, or is it different?

Since the quantity of stable element taken for activation ranges from 0.1 to 10 g., those radioactive elements formed which are isotopes of the same element as that used are mixed with the stable element. Those radioactive isotopes formed which have a different atomic number from that of the stable element bombarded are present in minute concentrations and as such can be chemically separated with or without addition of carrier, and the quantity of the latter may be controlled entirely by the requirements of the experiment. On this basis radioactive isotopes of different atomic number from that of the activated element are classified here as Group 1 tracers:

$$_zA^m \rightarrow {}_{z\pm1,2}A^{m\pm0,1,2}$$

that is, element A of charge number z produces upon activation radioactive isotopes of charge number $z \pm 1,2$; these first-group tracers, for the above reason, may be called "perfect tracers."

Radioactive isotopes of the same charge number as the activated element and, therefore, already diluted by the common element are classified here as Group 2 tracers:

$$_zA^m \rightarrow {}_zA^{m\pm1}$$
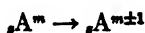
[2] The terms used in this paper are those generally accepted in the literature of nuclear physics. They are as follows: n for neutron; p for proton or hydrogen ion; d for deuteron or heavy hydrogen ion; α for alpha particle or helium ion. Nuclear reactions are expressed as follows:

$$_{29}Cu^{63} \ (d,p) \ _{29}Cu^{64}$$

meaning that when the isotope of copper of atomic number 29 and mass number 63 is bombarded with deuterons, a proton is ejected and the result is the formation of an isotope of copper having a mass number of 64.

That is, element A of atomic number z produces upon activation radioactive isotopes of the same atomic number z but of different mass, $m \pm 1$, from that of the stable isotopes bombarded.[3]

II. RELATIVE SIGNIFICANCE OF DIFFERENT RADIOACTIVE ISOTOPES AS TRACERS

The importance of obtaining radioactive isotopes, uncontaminated by considerable quantities of inactive elements, for the study of living organisms can be demonstrated with arsenic.

In figure 1 are shown the radioactive isotopes of arsenic which are important as tracers. The stable isotopes are shown by rectangles, and the radioactive isotopes are shown by ovals. Stable arsenic is a single isotope ($_{33}As^{75}$). Germanium consists of five stable isotopes. Within the rectangle for each stable isotope its abundance is given in per cent. The arrows indicate the nuclear reactions forming different radioactive isotopes. From this drawing it can be seen that, if germanium is activated with protons (p,n reaction), the radioactive isotope of arsenic ($_{33}As^{74}$) is formed from the stable isotope of germanium ($_{32}Ge^{74}$). The quantity of arsenic formed after several hours' bombardment in the cyclotron is very small (less than 10^{-8} g.), but all the atoms of arsenic present are radioactive and the intensity of radiation emitted during their disintegration is sufficient to make this isotope applicable as a tracer.[4]

The minute quantities of radioactive arsenic can be separated from germanium after addition of a small quantity of common arsenic as carrier. The added arsenic may be 1 mg. or even considerably less, depending entirely on the nature of the experiments to follow.

Arsenic itself can be activated by fast neutrons, the reaction being $_{33}As^{75}$ ($n,2n$) $_{33}As^{74}$. In this case the same radioactive isotope of arsenic will be formed as from germanium, but it will be mixed with 1 g. or even more of the common arsenic. This quantity of arsenic may be prohibitive for some studies of living organisms.

In table 1 are given different radioactive isotopes which fall into the Group 1 classification, the half-lives of which are long enough for experiments requiring considerable time. The half-life of each isotope, that is, the period in which the intensity of radiation and the number of radioactive atoms decreases by

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[3] A few attempts to separate newly formed radioactive isotopes of a given element from the stable isotopes of the same element have been made. The procedure known as the Szilard–Chalmers method, however, has not yet found practical application in trace element technique (32).

[4] During the activation of germanium with protons, other isotopes of arsenic ($_{33}As^{73,76}$) are also formed from other stable isotopes of germanium but these have shorter half-lives than As^{74}. The same active isotopes of arsenic can be obtained from germanium by d,n and $d,2n$ reactions.

There is no need of discussing in this paper all the possible nuclear reactions for forming active isotopes from germanium. The aim is to point out one particular nuclear reaction for the production of the best yield of a desired radioactive isotope, in order to facilitate the selection of a radioactive isotope which fits the duration of the subsequent biological experiment.
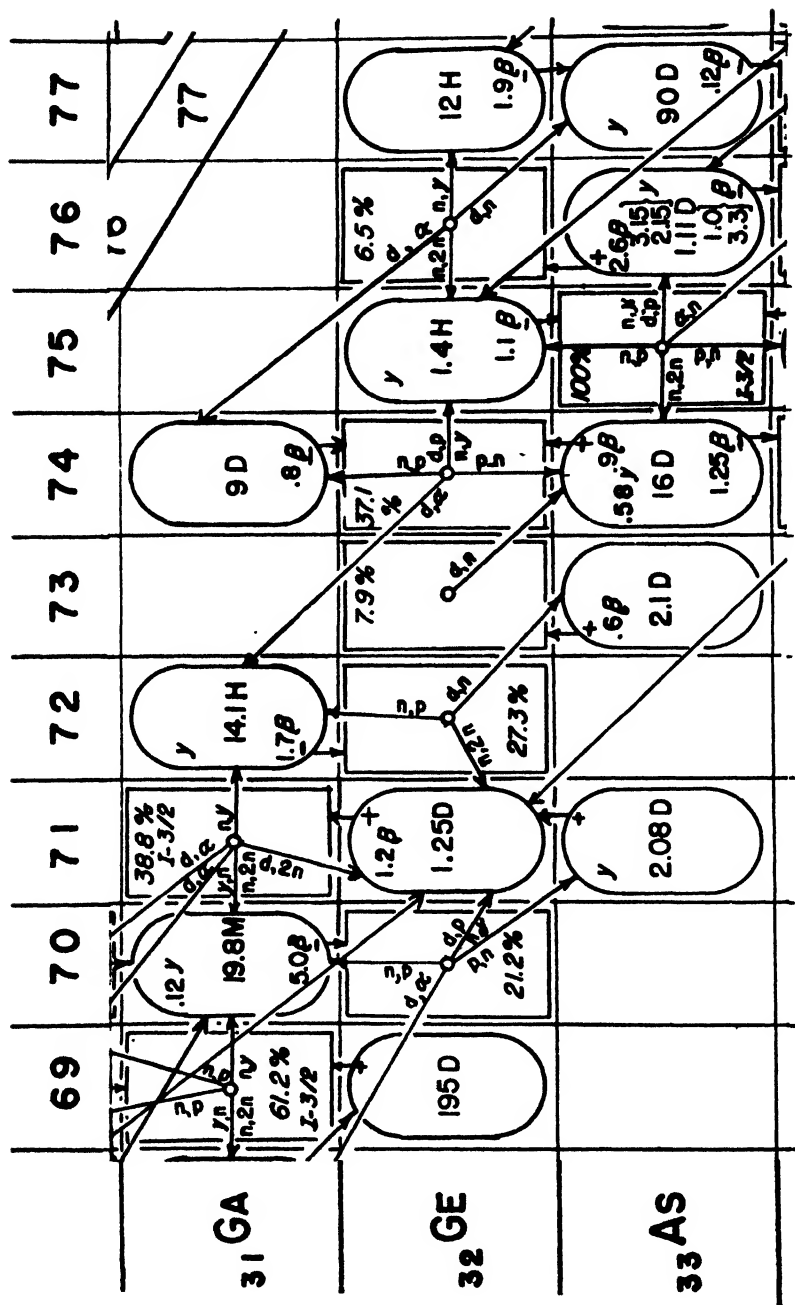
Fig. 1. Isotopic region of gallium, germanium, and arsenic

TABLE 1

Long-life tracers

Group 1: $_zA^m \rightarrow$ $_{z\pm1}A^{m\pm0,1,2}$

RADIOACTIVE ISOTOPE	HALF-LIFE	BOMBARDED STABLE ISOTOPE AND NUCLEAR REACTION	ENERGY OF β-RAYS	ENERGY OF γ-RAYS	RELATIVE YIELD	REFERENCES
	days		*Mev.*	*Mev.*		
$_{25}Mn^{52}$	7.4 D	Cr^{52} (p,n)	0.77 (+) K	0.90		(14)
$_{25}Mn^{54}$	310 D	Fe^{54} (d,α)	K	0.85 0.12	1*	(7)
$_{27}Co^{56,58}$	72 D	Fe^{54} $(d,2n)$ Fe^{57} (d,n) $Fe^{56,58}$ (p,n)	1.36 (+) 0.4 (+)	1.05 0.5 0.13 0.117		(23, 15)
$_{30}Zn^{65}$	250 D†	Cu^{65} $(d,2n)$	0.7 (+)	1.14	0.5	(22, 8)
$_{23}V^{48}$	16 D	Ti^{47} (d,n)	1.05 (+)	1.05		(35, 36)
$_{33}As^{74}$	16 D	Ge^{74} $(d,2n)$ Ge^{73} (d,n)	0.9 (+) 1.25 (−)	0.58	2	(7)
$_{33}As^{77}$	90 D	Ge^{76} (d,n)	0.12 (−)			(9)
$_{34}Se^{76}$	160 D	As^{75} (d,n)	K	0.3		(17, 37)
$_{39}Y^{88}$	105 D	Sr^{88} $(d,2n)$	K	1 92 0.95		(27, 18) (10, 13)
$_{47}Ag^{106}$ . . .	8.2 D	Pd^{106} (d,n)	K	1.63 1.06 0.50		(8)
$_{52}Te^{121}$	125 D	$_{51}Sb^{121}$ $(d,2n)$	K·	0.5		(30)
$_{53}I^{121}$	7.8 D	Te^{120} (d,n)	0.59 (−)	0.37 0.08	20	(7, 33)

* Data on relative yields are taken from a paper presented by Dr. J. G. Hamilton before the Conference on Applied Nuclear Physics, Massachusetts Institute of Technology, October 28, 1940. These data are tentative and subject to large fluctuations.

† This isotope can be produced by deuteron bombardment of the same element with better yield, but the radioactive atoms will be contaminated by the bulk of stable element taken for bombardment.

‡ Emitted electrons are shown as (−); emitted positrons as (+).

half, is given in the second column in days (D). The third column shows the nuclear reaction by which the radioactive isotope is produced. In the fourth and fifth columns are given the energies of radiation in millions of electron volts

(1 electron volt is equal to 1.59×10^{-12} ergs).[5] Most artificial radioactive nuclei emit electrons, positrons, or gamma rays. Some, however, disintegrate by capturing one of their electrons in the K shell. This less familiar disintegration process is designated as K. The electrons and positrons emitted by nuclei during their transmutation are known as beta rays. While the individual electrons composing beta rays possess different kinetic energies, the maximum energy is significant, because this upper limit energy characterizes individual radioactive isotopes. For this reason only the upper limit energy is given in the tables of beta disintegration.

The intensity of radiation is a very important factor in an estimation of the relative value of radioactive isotopes as tracers. Thus, if disintegration occurs with emission of electrons $(-)$ or positrons $(+)$ with energy of more than a million electron volts the detection of radiation is very simple and such radiation may be classified conditionally as strong. Electrons emitted with an energy of between two hundred thousand and a million electron volts may be called medium energy electrons, and elements emitting electrons with an energy of one hundred thousand or less electron volts may be said to have weak radiation. Gamma rays, like x-rays, are electromagnetic and therefore can not be measured directly as the corpuscular types of radiation (for example, beta radiation which ionizes gases). However, gamma rays will eject electrons from molecules of gases, and these in turn produce ionization which is measurable.

Most of the isotopes shown in table 1 have already been used as tracers in various biological problems. Outstanding among these is the work with radioactive iodine on thyroid physiology and the distribution of iodine in normal and diseased thyroids.

The desirable duration of an experiment can be estimated on the basis of the half-life and relative yields of activities: for instance, for Mn^{54}, two half-lives, that is, a period of the order of 600 days; for Zn^{65}, one half-life or about one year; and for arsenic, three half-lives or about 48 days.

The considerable interest at present in the significance of traces of zinc in living organisms justifies more detailed description of the possibility of studying these phenomena with radioactive isotopes of zinc.

From figure 2 it can be seen that a long-life isotope of zinc can be produced by bombardment of zinc with deuterons ($_{30}Zn^{64}$ (d,p) $_{30}Zn^{65}$) or by bombardment of copper with deuterons or protons ($d,2n$ or p,n reactions). The yield of active zinc is considerably better when zinc is bombarded. However, in this case it is mixed with a large bulk of inactive zinc, while if copper is bombarded, the zinc added as carrier for separation of the active zinc can be limited to a desired ratio.

In case the tracer studies can be completed in 2 days it is sensible to limit the experiments to that time in order to use the isotope of zinc of shorter half-life,
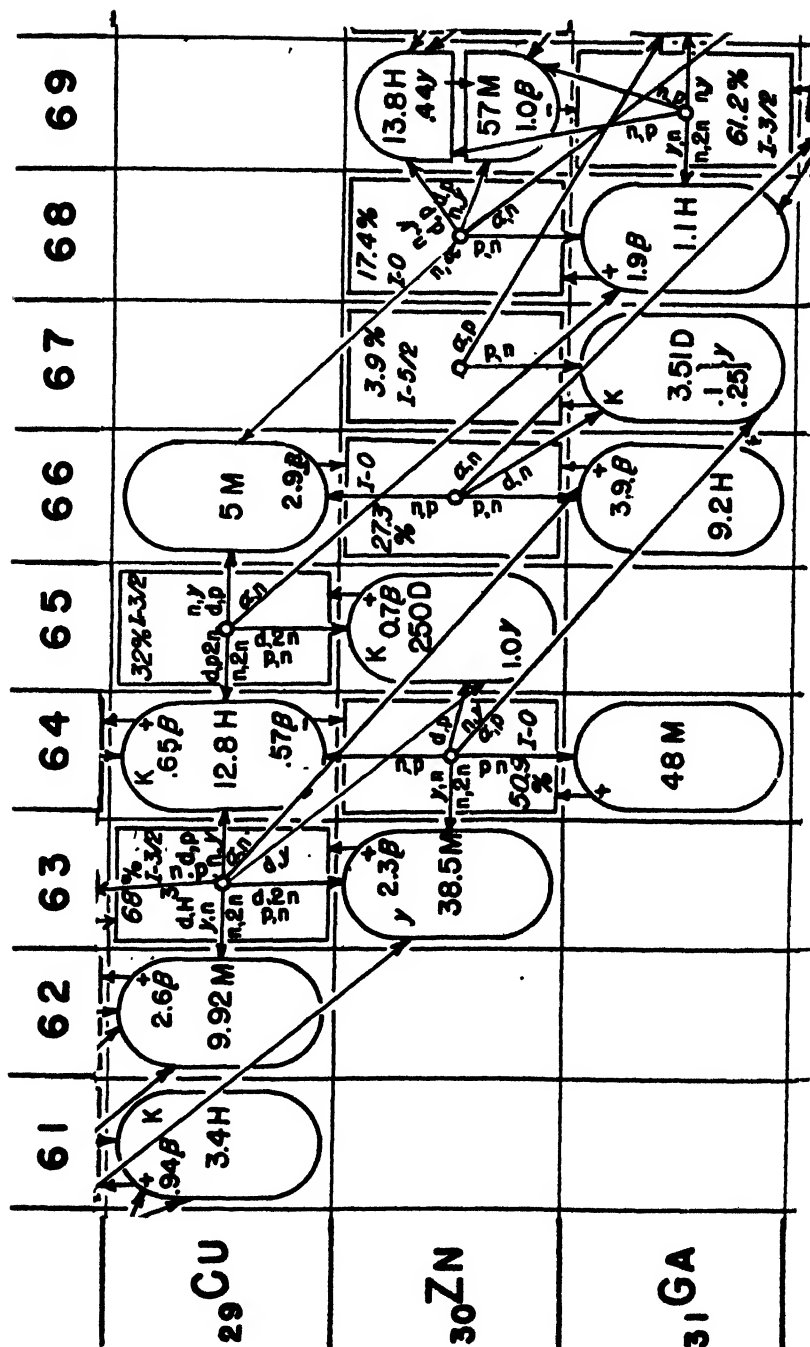
FIG. Isotope region copper and lium

because of its greater intensity of radiation. In this connection it may be said that, in general, the activity of a long-life isotope is weaker than that of a short-life isotope when they have similar types of radiation.

An additional consideration in planning tracer studies is the extent of distribution of the element, say zinc, through the whole body of the living organism, as compared to the amount in that part of the organism actually undergoing measurement. This is more of a limiting factor in the application of a long-life

TABLE 2

Intermediate-life tracers

	TIVE PE.	HALF-LIFE	BOMBARDED STABLE ISOTOPE AND REACTION	ENERGY OF β-RAYS	ENERGY OF γ-RAYS	TRACER GROUP	REFERENCES
		hours		*Mev.*	*Mev.*		
$_{27}Co^{55}$	.	18.2 H	Fe^{54} (d,n)	1.5 (+)	1.2 0.8	1	(20, 22)
$_{29}Cu^{64}$	.	12.8 H	Cu^{63} (d,p)	0.58 (−) 0.66 (+) K		2*	(31, 34)
$_{30}Zn^{69}$	.	13.8 H† 57 M†	Zn^{68} (d,p)	1.00 (−)	0.44	2	(16, 22)
$_{33}As^{76}$..	.	26.7 H	As^{75} (d,p)	3.24 (−)	2.05	2	(24)
$_{35}Br^{82}$..		36 H	Br^{81} (d,p)	0.46 (−)	1.35 0.79 0.55	2*	(28)
	.	12.6 H	Te^{130} $(d,2n)$	1.07 (−) 0.55 (−)	0.74 0.67 0.53 0.42	1	(7, 9)

* These isotopes can be obtained as tracers of Group 1 from the element of previous charge number but in lower yield.

† Isomers: M indicates half-life in minutes.

isotope of weak radiation than it is for a short-life isotope with strong radiation, for the latter can be detected locally even after wide distribution in the body.

The last isotope of zinc shown on the chart, with a half-life of 13.8 hr., can be obtained by activation of zinc with deuterons and, of course, is contaminated with inactive zinc. This active isotope, Zn^{69}, does not disintegrate directly to gallium but first produces another radioactive isotope of the same mass (nuclear isomer) but with a half-life of only 57 min. The latter disintegrates into gallium with emission of electrons having an energy of one million electron volts. As long as the 13.8-hr. isotope exists, the 57-min. isotope is present too. Thus two

radiations, gamma and beta,—the first emitted by the 13.8-hr. period and the second by the 57-min. period,—will be observed together.

In table 2 are given the radioactive isotopes of different elements having half-lives similar to that of Zn^{69}. In all cases in which experiments can be completed in not more than 3 days and do not require minute quantities, that is, 10^{-4} g. or less, these isotopes should be selected, even though some of the elements have active isotopes of longer half-life. The reason for this is that the yields in terms of activity units are many times greater than those of the elements in table 2. The radioactive isotopes of copper and bromine shown in the table have the longest half-lives known for these elements today.

The next series of radioactive isotopes (see table 3) consists of tracers with half-lives which require completion of · an experiment within 24 hr. These

TABLE 3

Short-life tracers

Group 2: $_zA^m \rightarrow {}_zA^{m+1}$

RADIOACTIVE ISOTOPE	HALF-LIFE	BOMBARDED STABLE ISOTOPE AND REACTION	ENERGY OF β-RAYS	ENERGY OF γ-RAYS	REFERENCES
	hours		*Mev.*	*Mev.*	
$_{25}Mn^{56}$ ..	2.59 H	Mn^{55} (d,p)	2.8 (−) 1.15 (−)	2.2 0.83	(1, 7, 11)
$_{28}Ni^{63}$ ..	2.60 H	Ni^{62} (d,p)	1.65 (−)	0.93 0.65 0.28	(11)
$_{56}Ba^{139}$ . ..	1.42 H	Ba^{138} (d,p)	1.0 (−)	0.6	(26)
$_{14}Si^{31}$	2.60 H	Si^{30} (d,p)	1.37 (−)		(8, 25, 38)

isotopes, which have a very strong intensity of radiation, are produced by short bombardment. They belong to the second group of tracers, with the exception of Mn^{56}, which can be produced by activation of chromium. For experiments of a type which can be performed in small volumes, that is, of the order of 100 cc., there are radioactive isotopes of chromium, nickel, and barium of longer half-life. These can be obtained as tracers of the first group but of rather weak radiation.

From figure 3 it can be seen that the radioactive isotope of nickel, Ni^{57}, is obtained by activation of iron with alpha particles. This isotope is produced in minute concentrations of half-life 1.5 days. The relative yield and intensity of radiation are rather moderate. By activation of titanium with alpha particles, the 26.5-day radioactive isotope of chromium can be secured in minute concentrations. Bombardment of cesium with deuterons yields the active isotope of barium of half-life 39.5 hr. (4).

The last series of radioactive isotopes, given in table 4, are of rather short life, but their use as tracers is of considerable value in the solution of problems the
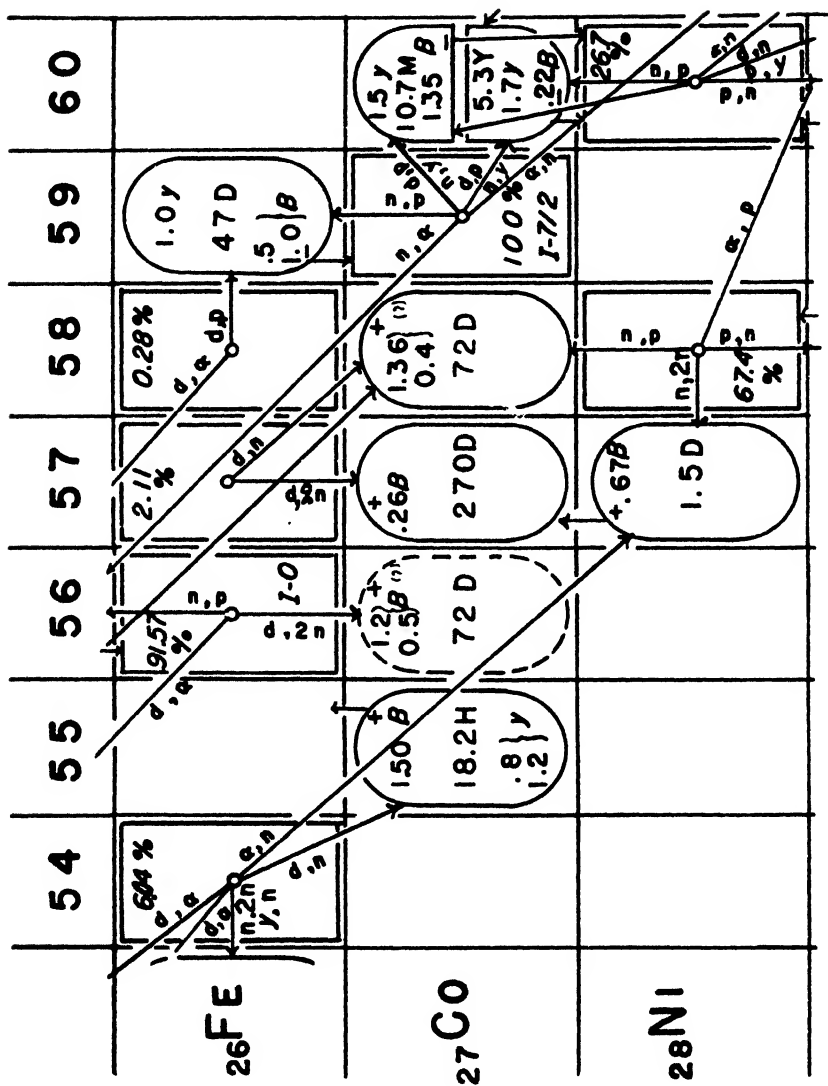
Fig. 3. Isotopic region of iron, cobalt, and nickel

duration of which is not more than several hours. All these isotopes are first-group tracers and can be secured with strong intensity of radiation. In addition, the radioactive isotope F^{18}, with half-life 1.9 hr., is the longest known isotope of the element fluorine.

TABLE 4

Short-life tracers

Group 1: $_zA^m \rightarrow {}_{z+1}A^{m+0,1}$

RADIOACTIVE ISOTOPE	HALF-LIFE*	BOMBARDED STABLE ISOTOPE AND REACTION	ENERGY OF β-RAYS	ENERGY OF γ-RAYS	REFERENCES
			Mev.	*Mev.*	
$_9F^{18}$	1.9 H	O^{18} (p,n)	0 74 $(-)$		(6)
$_{25}Mn^{51}$	46 M	Cr^{50} (d,n)	2.0 $(-)$		(21)
$_{30}Zn^{63}$	38.5 M	Cu^{63} $(d,2n)$	2.3 $(-)$	γ	(31)
$_{34}Se^{75}$ . . .	1.81 H	As^{75} (p,n)	β $(+)$		
$_{53}I^{128}$ . . .	25 6 M	Te^{128} $(d,2n)$	2 44 $(-)$	0.4	(33)

* H = hours; M = minutes.

† Can be obtained as tracer of the second group by activation of iodine with deuterons.

III. INDIRECT TRACERS

From the above review of different groups of radioactive isotopes it is obvious that not all trace elements in living organisms have radioactive isotopes suitable to be used as tracers. Thus, aluminum, magnesium, lithium, and boron have no active isotopes of sufficiently long life to be used as tracers in biological experiments. The longest lived isotope of aluminum has a half-life of only 6.7 min., that of magnesium a half-life of 10.0 min., that of lithium a half-life of 0.89 sec., and that of boron a half-life of only 0.02 sec. In such cases as these it is justifiable to use indirect tracers, that is, radioactive isotopes of chemically similar elements.

Gallium is similar to aluminum and has two radioactive isotopes; Ga^{66}, 9.2 hr. half-life and strong positron radiation; Ga^{67}, 84.4 hr. of 0.25 Mev. gamma radiation. Both are isotopes of Group 1 and are easily produced simultaneously by activation of zinc with protons (see figure 2) (2, 3).

The isotope of silicon has a rather short half-life of 2.6 hr., but the chemically similar element germanium has several isotopes with long half-lives. For example, Ge^{71}, produced by deuteron bombardment of gallium, belongs to the Group 1 tracers and is a strong emitter of positrons (see figure 1) (23).

In table 5 are given radioactive isotopes of Group 2 which are of long life and have strong radiation. These have already been applied as indirect tracers. It might be mentioned that Sr^{89} has been used as a tracer for calcium in the solution of biological problems, since the long-life radioactive isotope of calcium, Ca^{45}, has weak intensity of radiation. Similarly, rubidium can be used to trace potassium when the 12.4-hr. period of K^{42} is not sufficiently long (10, 12, 13, 18).

For a comparative study of the effects of light and heavy elements of the same periodic group, radioactive isotopes of sulfur, selenium, and tellurium may be

used as examples. The isotopic region of tellurium is shown in figure 4, from which it is evident that a variety of isotopes are available.

Sulfur has a long-life isotope with a half-life of 88 days. However, it has a rather weak electron radiation—0.107 Mev.—which requires a somewhat different condition of measurement.

For a comparative study of the elements iron, nickel, and cobalt, suitable radioactive isotopes of cobalt (shown in figure 3) can be selected for experiments of various lengths (5, 15, 23).

TABLE 5

Long-life tracers

Group 2: $_zA^m \rightarrow {}_zA^{m+1}$

RADIOACTIVE ISOTOPE	HALF-LIFE	BOMBARDED STABLE ISOTOPE AND REACTION	ENERGY OF β-RAYS	ENERGY OF γ-RAYS	RELATIVE YIELD*	REFERENCE
	days		*Mev.*	*Mev*		
$_{22}Ti^{51}$	72 D	Ti^{50} (d,p)	0.36 (−)	1.00		(31)
$_{37}Rb^{86}$	19.5 D	Rb^{85} (d,p)	1.50 (−)		10	(13)
$_{38}Sr^{89}$	55 D	Sr^{88} (d,p)	1.50 (−)		7	(10)

* Relative yield is given in the same units as in table 1.

IV. DETERMINATION OF TRACE ELEMENTS BY MEANS OF RADIOACTIVE TRACERS AND TECHNIQUE OF MEASUREMENTS

A quantitative determination of any element in any of its chemical compounds by means of radioactive tracers is based on acceptance of the fact that radioactive isotopes mixed homogeneously with inactive isotopes of the same chemical element will accompany the stable element, always being in the same ratio as in the initial mixture, so long as no conditions for separation of isotopes are involved.

From this statement it follows at once that there is no necessity (except in some specific cases) for knowing the actual weight of the radioactive isotope added. It is, however, necessary to know the total weight of the stable element and the radiation of the added active isotope.

At the present time the intensity and nature of radiation, that is, whether the radiation is corpuscular or electromagnetic, can be determined with equal simplicity by means of two main types of instruments: (*1*) the electrometer and (*2*) counters.

An electrometer measures with great exactness the ionization produced by the radiation as a whole or a summarized effect from all particles penetrating into the ionization chamber from the active source. Consequently, the geometrical arrangement of a solid active substance with regard to the ionization chamber is of primary significance when the reproducibility of experiments with the same intensity of radiation is required, as in many biological problems.

In figure 5 is shown a typical arrangement of a unifilar electrometer with ionization chamber on top, for measurement of solid radioactive substances.
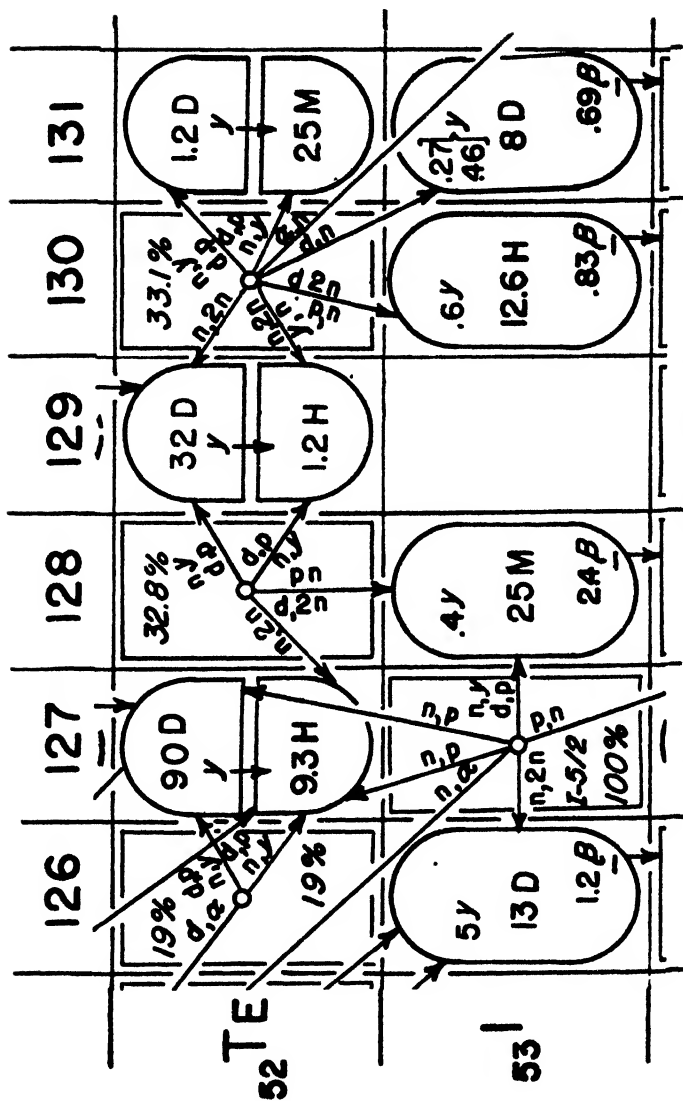
Fig. 4. Isotopic region of tellurium and iodine

From the diagram one can see that the batteries, through resistances, are connected to the plate P of the electrometer and to the inner cylinder A of the ionization chamber I. When rod r of the ionization chamber is disconnected from the ground and the gas in the chamber is ionized, the rod will become charged. The fiber of the electrometer which is connected to the rod will then move toward the appropriately charged plate P, to the left in this diagram. With proper strength potential applied to the cylinder of the ionization chamber, the
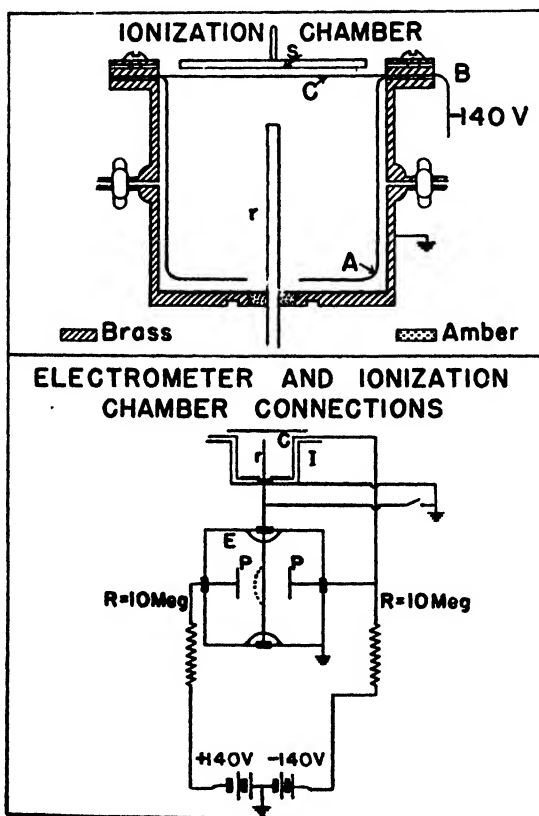
FIG. 5. Arrangement of unifilar electrometer

velocity of the fiber in the electrometer will be proportional to the ionization current obtained in the chamber and this current, at saturation, is proportional to the intensity of ionization produced by the radioactive sample.

The ionization chamber shown in the upper part of figure 5 has a thin aluminum window, C, supporting sample S of radioactive substance. The diameter of sample S, its thickness, and even the bulk of the material within it are of great significance in obtaining the same results with identical samples. The time required for preparing geometrically identical solid samples prohibits the use

of the electrometer in many cases and results in a real advantage in the use of Geiger Muller counters,

The general recognition of Geiger Muller counters as the instruments best fitted for measuring radiations in tracer studies is well founded upon its convenience and speed of operation. In figure 6 is shown a general diagram of a Geiger Muller counter and in figure 7 a picture of part of a counter tube. The counter tube consists of a closed glass cylinder filled with a mixture of air and argon, or sometimes with other gases, at a pressure of several centimeters of mercury. The cylindrical part of the tube is made of very thin glass which permits electrons to penetrate if they have sufficient kinetic energy. The inside of the tube is covered with either a very fine deposit of some metal or its oxide or has just a metal screen. A tungsten wire is sealed into the glass at the bottom and the top of the tube. The wire usually is charged positively and the metal wall negatively.

The principle of operation of the counter consists in the following: Until the potential difference between the wire and the plated metal attains a definite
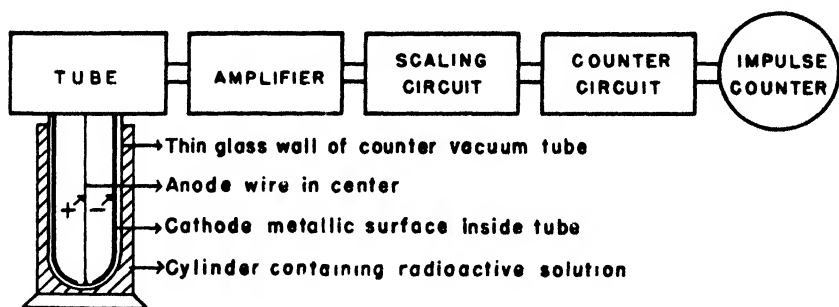

FIG. 6 Diagram of Geiger Muller counter

value, depending upon the dimensions, the inner gas, and its pressure, etc., no discharge takes place even if some radioactive substance is placed near the counter tube. When the potential is raised to a definite value, known as the threshold voltage, a discharge takes place in the presence of a radioactive substance. One particle, such as an electron with sufficient kinetic energy, penetrating the tube is sufficient to produce a discharge. The discharge or count is transmitted through an amplifier and counter circuit to the impulse counter, which registers the discharge on a watch-type dial.

As soon as a discharge occurs, the potential through the tube drops to some low value at which (by means of radio tubes connected to the counter tube, shown in figure 7) the discharge is extinguished and the potential across the counter tube recovers its initial value. The quenching of discharge and recovery of potential of the tube can be obtained by partially filling the tube with alcohol or some other volatile organic compound, with an action similar to that of the radio tube quenching circuit. The resolving time of the tube, that is, the time which is required for discharge and recovery, in a properly constructed tube is very small, of the order of 10^{-4}

From this figure it is evident that a counter tube is capable of producing many thousand discharges per minute. However, mechanical counters are able to register only several hundred pulses per minute. If the source of radiation is too strong, a special circuit, known as a scaling circuit, is included in the counting system. The scaling circuit facilitates the work of the impulse counter by delivering only a definite fraction of the total discharge per minute. Frequently the scaling circuit is so made that only each sixteenth discharge will be registered by the impulse counter.
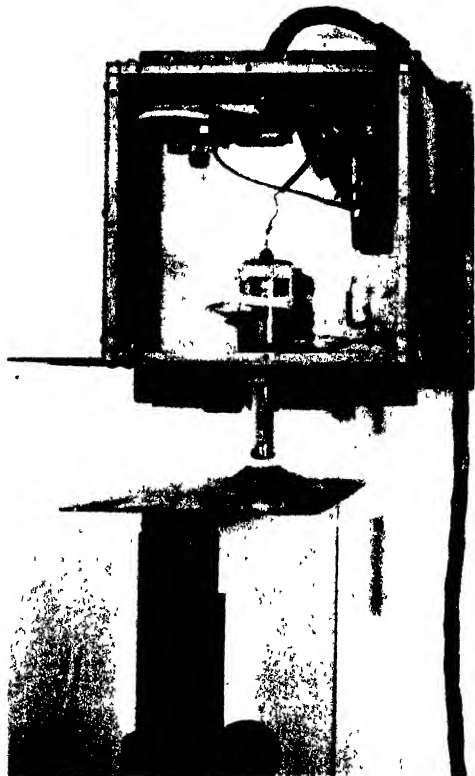
FIG. 7. Geiger–Muller immersion tube with cylinder containing radioactive solution

From this description it can be seen that, in contrast to the electrometer, which measures the total ionization effect of all particles penetrating the ionization chamber, a Geiger–Müller counter tube registers the number of individual atomic disintegration particles that enter the tube. However, the reproducibility of the geometrical position of a sample in regard to the Geiger–Müller tube is just as important as with the electrometer. The principal advantage of a Geiger–Müller counter is that it may be used with liquid samples. Liquid samples in many experiments are readily obtained, and in such cases a Geiger–Müller tube can be immersed directly in liquid.

As is shown in figures 6 and 7, the displacement of liquid by the counter tube is always the same and the geometrical conditions are easily reproducible, provided the volume of liquid is kept constant. Furthermore, the time required for preparation of solid samples is eliminated. As shown in figure 7, the proper displacement of liquid is obtained by a graduated lift table. The graduated cylinders used for the radioactive substances have always the same diameter.

The reliability of a Geiger-Müller counter depends upon several characteristics. The first of these is the stability and range of the plateau of the counter, that is, the range of voltage at which the counter delivers the same number of counts for a given activity of sample. For example, a satisfactory counter tube may start operating at 1200 volts, have a plateau from 1200 to 1500 volts, and only above 1500 volts show an anomalous increase in the number of counts. With a typical background count of about twenty counts per minute (number of counts delivered by Geiger-Müller counter in the absence of any radioactive substance), a liquid sample containing a radioactive substance and producing not less than two hundred counts per minute provides reproducible results.

In conclusion the proper procedure with tracers can be illustrated by two examples:

(1) Assume that the first problem is stated as follows: The effect of nickel (in the form of one of its salts) on some organisms is to be studied. The duration of the experiments is only several hours and the quantity of common nickel present must be strictly controlled and is not to exceed 1 mg. per experiment. The last condition prohibits the use of Ni^{63}, since a large quantity of a stable nickel will be mixed with the radioactive Ni^{63}. The nickel isotope Ni^{57}, 1.5 days, fits the requirements better because it is a Group 1 tracer and can be separated from the bombarded iron with proper quantities of stable nickel.

Thus, having obtained the solution of nickel salt with the desired concentration of nickel, a 10-ml. sample should be set aside for measurement of activity from time to time to follow the disintegration curve. From the disintegration curve the ratio of the number of counts to the quantity of stable nickel can be obtained for each time at which the biological experiments are measured. This example demonstrates favorable conditions for supplying radioactive tracers of the first group having weak intensity of radiation.

(2) The second problem can be presented as follows: A living organism having a total weight of 1 kg. is to be studied with regard to the distribution and concentration of manganese in different parts of the body. The duration of the experiment is to be 100 days and 50 g. of the body are to be removed for study.

For this work the radioactive isotope of manganese Mn^{54}, 310 days, can be considered suitable. It is obtained by activation of iron with deuterons. The manganese so formed is separated from iron by the usual analytical procedures and purified, using iron, cobalt, and other carriers in order to obtain the manganese in a pure radioactive state.

A part of the manganese salt so prepared should be measured on a Geiger-Müller counter and the activity followed for a few weeks to make sure that the period of disintegration corresponds to that of Mn^{54}. The established ratio (counts of activity)/(grams of stable manganese) at the beginning of the experi-

ment and in the analyzed material at the end should be sufficiently high to permit accurate radioactive measurements.

It may now be concluded that, in order successfully to apply radioactive isotopes as tracers, it is necessary (*1*) to determine the duration of the experiment, (*2*) to find out if a suitable radioactive isotope exists, and (*3*) to evaluate the experimental conditions in regard to the optimum ratio of intensity of radiation in counts to the quantity of inactive traced element in grams.

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ORGANIC COMPOUNDS OF POLYVALENT IODINE

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The present review gives particular emphasis to recent work done in the field of organic compounds of polyvalent iodine. A brief historical survey is presented. The remainder of the survey deals with iodoso, iodoxy, and iodonium compounds under the following headings: (a) preparation; (b) properties; and (c) structures.

Phenyl iodide is a very interesting compound because of the polyvalency of its iodine atom. When it is treated with dry chlorine in anhydrous inert solvents, yellow crystalline phenyliodoso chloride, $C_6H_5ICl_2$, is formed. With bases the latter compound forms iodosobenzene or phenyliodoso oxide, C_6H_5IO. When iodosobenzene is heated, it undergoes disproportionation to give phenyl iodide and iodoxybenzene, $C_6H_5IO_2$. Treatment of iodosobenzene with phenylmagnesium bromide, or with silver oxide and iodoxybenzene, produces diphenyliodonium hydroxide, $(C_6H_5)_2IOH$, a strong base.

There is in existence, therefore, a group of organic iodides in which the halogen atom can exert a valence greater than one. Most of the work on compounds of polyvalent iodine was done between the years 1892 and 1912. During the past thirty years there has appeared only occasional reference to this group, a group certainly of considerable theoretical interest, especially from the standpoint of valence studies. The object of this paper is to discuss in a general way this group of compounds and to review the more important work done since 1914. The excellent monograph written by C. Willgerodt (85) and published in 1914 covers in detail the earlier work accomplished in this field, and no attempt has been made to repeat what has already been done.

I. HISTORICAL

In 1885 Willgerodt (86) prepared phenyliodoso chloride, $C_6H_5ICl_2$, the first organic compound containing polyvalent iodine to be recorded. The compound was obtained by the action of iodine trichloride on phenyl iodide. One year later, in 1886, Willgerodt (89) discovered that the same compound could be prepared by passing chlorine through a solution of phenyl iodide in chloroform, under which conditions it separated as light yellow needles.

In 1892 Meyer and Wachter (50) prepared o-iodosobenzoic acid by the oxidation of o-iodobenzoic acid with fuming nitric acid. This was the first iodoso compound to be discovered. In the same year Willgerodt (75) obtained iodosobenzene, C_6H_5IO, by treating phenyliodoso chloride with an aqueous solution of sodium hydroxide, and in the same report he mentioned the preparation of iodoxybenzene, the first iodoxy compound, by heating iodosobenzene.

Meyer and Wachter (50) in describing iodosobenzoic acid, the first iodoso compound, suggested the possibility of making aromatic iodoxy compounds by

treating aromatic compounds with sulfuric acid and iodic acid, the latter acid corresponding to nitric acid. They actually added benzene to the mixture of acids and got a solid compound. However, it does not appear that the experiment was followed up. It was not until 1937 that Masson and Race (45) showed that in a number of cases this reaction, instead of producing the iodoxy compound, affords much the simplest and most economical way of making iodonium compounds.

In 1894 Hartmann and Meyer (25) dissolved iodosobenzene in cold concentrated sulfuric acid and so were the first ones to discover the existence of the remarkable class of polyvalent iodine compounds known as iodonium compounds. They showed that the reaction mixture contained the sulfate of the base, phenyl-*p*-iodophenyliodonium hydroxide, a derivative of the hypothetical base, H$_2$IOH. Later in the same year, Hartmann and Meyer (26) obtained diphenyliodonium hydroxide by shaking equivalent quantities of iodosobenzene and iodoxybenzene with water and silver oxide. Mixed aliphatic aromatic iodonium compounds were prepared by Willgerodt (80, 87) in 1895 by the action of aryliodoso chlorides on the compound of silver chloride and silver acetylide suspended in water. These compounds were described by Willgerodt as being dichloroethylaryliodonium compounds. It remained for Thiele and Haakh (65) to show that the compounds described by Willgerodt were dichlorovinyl compounds and not dichloroethyliodonium compounds. It also remained for Thiele and Haakh (65) to show that organic compounds of polyvalent iodine are not peculiar to the aromatic series. They found analogs to all of these compounds amongst the olefins, with chloroiodoethylene as their simplest parent substance. Thiele (66, 67) even demonstrated that methyl iodide at low temperatures could combine with chlorine. However, the product decomposed readily at $-28°C.$, producing methyl chloride and iodine chloride. To have a stable compound of polyvalent iodine it was therefore necessary to have this element attached to a doubly bound carbon atom.

Many of the fundamental properties of the iodoso, iodoxy, and iodonium groups have remained obscure or else misapprehended since the pioneering discoveries of Willgerodt and Victor Meyer. However, the relatively recent and excellent contributions made by J. R. Johnson, Lucas and coworkers, Masson and coworkers, and others have done much to throw light on these groups and the relations which exist between them.

II. PREPARATION OF THE COMPOUNDS OF POLYVALENT IODINE

A. Iodoso compounds

Willgerodt (76, 79) and V. Meyer (2) obtained iodoso compounds readily by treating an iodoso salt, such as the iodoso chloride, with a dilute aqueous solution of an alkali hydroxide, an alkali carbonate or bicarbonate, calcium hydroxide or barium hydroxide:

$$C_6H_5ICl_2 + 2NaOH \rightarrow C_6H_5IO + H_2O + 2NaCl$$

It was found advisable to use aqueous sodium carbonate or bicarbonate instead of the alkali hydroxide for the preparation of the iodoso compounds from poly-

halogen-substituted phenyliodoso chlorides (97). Thiele and Haakh (85) used the alkali carbonates instead of the alkali hydroxides for the preparation of the iodoso compounds from iodoethylene iodoso chloride and chloroethylene iodoso chloride. Lucas, Kennedy, and Formo (38) have given directions for the preparation of iodosobenzene in a 60 to 62 per cent yield, by the action of aqueous sodium carbonate and sodium hydroxide on phenyliodoso chloride. Ortoleva (54) prepared iodoso compounds by the action of water on a pyridine solution of the iodoso chloride.

Iodoso compounds have been made by the direct oxidation of the organic iodide. V. Meyer and coworkers (2, 50) used fuming nitric acid or potassium permanganate in dilute sulfuric acid as the oxidizing agent. Harries (23) oxidized phenyl iodide to iodosobenzene by means of ozone. Böeseken and Schneider (5, 6) carried out the oxidation of aromatic iodine compounds with 8 to 10 per cent solutions of peracetic acid in acetic acid. In no case did the oxidation proceed beyond the iodoso stage. The acetates of the following compounds were thus prepared: iodosobenzene, o-iodosotoluene, o-nitroiodoso-benzene, m-nitroiodosobenzene, and p-iodosobenzoic acid. Similarly, m-diiodosobenzene tetraacetate was obtained from m-diiodobenzene and o-diiodoso-benzene anhydride diacetate from o-diiodobenzene. Under similar conditions o-iodobenzoic acid and o- and p-iodobenzenesulfonic acids gave the corresponding iodoso compounds, which were believed to be internal salts without ring structure. With a 70 per cent solution of peracetic acid, monoiodofumaric acid gave iodosofumaric acid, which lost carbon dioxide in boiling water to form iodosoacrylic acid. Diiodofumaric acid took up two oxygen atoms, probably yielding the diiodoso acid, which lost no carbon dioxide in boiling water. Arbuzov (1) also reported the oxidation of phenyl iodide to the iodoso state by means of peracetic acid and perbenzoic acid.

Masson and Hanby (44) have carried out the direct substitution of aromatic hydrogen by the iodoso group, by the use of iodyl sulfate, $I_2O_3 \cdot SO_3$ or $(IO)_2SO_4$. The latter reagent was prepared from iodine, iodine pentoxide, and 96 per cent sulfuric acid. Nitrobenzene gave a 50 to 60 per cent yield of m-iodosonitro-benzene. Benzenesulfonic acid similarly gave iodosobenzenesulfonic acid and benzoic acid was likewise attacked, although with complications. In the direct formation of m-iodosonitrobenzene the missing 40 to 50 per cent yield was accounted for as m-iodonitrobenzene and iodonium salts. These products were experimentally traced to a relatively slow secondary decomposition of the primary iodoso compounds by sulfuric acid. The secondary decomposition was of the same kind as that discovered by Hartmann and V. Meyer (25) who, by treating iodosobenzene with concentrated sulfuric acid, obtained p-iodophenyl phenyliodonium sulfate, together with degradative consumption of oxygen and the formation of iodo compounds. Theirs was a rapid reaction, but in the case of the m-iodosonitrobenzene the m-nitro group made the decomposition slow and thus the m-iodosonitrobenzene was easily isolated before much of it was consumed.

Masson and Hanby, in their interpretation of the reaction, have considered it as being a number of ionic exchanges between the following ions: IO^+, iodyl;

I^{+++}, iodous; RI^{++}, iodoso; and R_2I^+, iodonium. The iodyl sulfate was regarded as the source of I^{+++} cations:

$$IO^+ + 2H^+ \rightleftarrows I^{+++} + H_2O$$

The formation of m-iodosonitrobenzene was expressed as a partial ion exchange:

$$I^{+++} + RH \rightarrow H^+ + RI^{++}$$
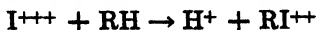
and, apart from the slow secondary decomposition, the reaction with a reagent which contained a m-directing substituent stopped there. With a compound containing an o,p-directing substituent the same reaction was considered to take place but was followed by a further step in ionic exchange:

$$RI^{++} + RH \rightarrow H^+ + R_2I^+$$
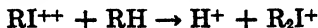
the total reaction being therefore

$$I^{+++} + 2RH \rightarrow 2H^+ + R_2I^+$$
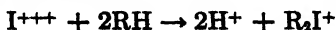
It might be mentioned here that some of the above ions such as the iodous ion, I^{+++}, are unusual and interesting ions and lend themselves to much speculation.

B. Iodoso salts

Willgerodt (75) showed that one of the best methods for the preparation of the iodoso chloride was to lead dry chlorine gas into an ice-cold solution of the aryl iodide dissolved in chloroform, the reaction being analogous to the behavior of iodine monochloride:

$$ICl + Cl_2 \rightarrow ICl_3$$

$$C_6H_5I + Cl_2 \rightarrow C_6H_5ICl_2$$
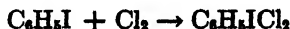
Under these conditions the salt separated as a crystalline mass. If crystallization did not occur, the addition of low-boiling ligroin generally brought it about. Carbon tetrachloride, carbon disulfide, glacial acetic acid, and benzene were also used as solvents. The iodoso chlorides of benzene, of alkyl-, bromo-, chloro-, and nitro-substituted benzenes, and of naphthalene have been prepared in this way. The presence of several negative groups in the aromatic nucleus appears to prevent the addition of chlorine to the iodo group, for no iodoso chloride has been isolated from penta- and tetra-chloroiodobenzenes (97). Lucas and Kennedy (36) have prepared phenyliodoso chloride in 87 to 94 per cent yield by treating phenyl iodide in dry chloroform with chlorine at the temperature of an ice–salt mixture. The three tolyliodoso chlorides were prepared in good yields by similar methods. In order to prepare an alkyliodoso chloride, Thiele and Peter (66) worked at the temperature of liquid air or of a mixture of dry ice and ether. Töhl (68) used sulfuryl chloride as a source of chlorine. Satisfactory results were obtained by this method with phenyl iodide, p-tolyl iodide, 1,3,4-triiodo-m-xylene, and iodomesitylene. Willgerodt (75, 78) made iodoso chlorides by the action of hydrochloric acid on the corresponding iodoso or iodoxy compounds:

$$C_6H_5IO + 2HCl \rightarrow C_6H_5ICl_2 + H_2O$$

$$C_6H_5IO_2 + 4HCl \rightarrow C_6H_5ICl_2 + 2H_2O + Cl_2$$

p-Tolyliodoso fluoride (20) was prepared from p-iodosotoluene and 46 per cent hydrofluoric acid in acetic acid. This compound was used for fluorinating because it was an easily purified solid, it could be prepared and used in glass apparatus, and its chloroform solution was stable for several days.

By dissolving iodoso compounds in glacial acetic acid, the acetates have been obtained. Similarly, salts of other organic acids, such as formates, propionates, and benzoates, have been prepared. Nitrates have been made by treating iodoso compounds with dilute nitric acid; chromates by the addition of chromium trioxide to acetic acid solutions of the iodoso compounds. Basic salts have been obtained from aryliodoso compounds containing several negative substituents in the nucleus (78, 97).

C. Iodoxy compounds

Willgerodt (77) reported the preparation of iodoxy compounds by heating the corresponding iodoso compounds:

$$2C_6H_5IO \rightarrow C_6H_5I + C_6H_5IO_2$$

The heating was generally done in the presence of water, so that steam distillation could be carried out. The organic iodide which was produced by dismutation was carried over by the steam, the iodoxy compound being left behind. The latter was then crystallized from water, acetic acid, or formic acid. Lucas and Kennedy (37) have given directions for the preparation of iodoxybenzene in 92 to 95 per cent yield by the rapid steam distillation of iodosobenzene.

Hartmann and Meyer (24) found that o-iodosobenzoic acid, which did not undergo dismutation on heating, could be oxidized to o-iodoxybenzoic acid with alkaline potassium permanganate.

The method of preparing an iodoxy compound by heating the iodoso compound is not entirely satisfactory, because one half of the latter goes back into the state of the iodo compound. To overcome this difficulty Willgerodt (81) oxidized the iodoso compound directly to the iodoxy compound with hypochlorous acid, bleaching powder solution, or sodium hypochlorite. He also found that the iodoso chloride could be oxidized with sodium hypochlorite or with bleaching powder. A convenient method was to chlorinate the iodo compound in water; sodium hydroxide was then added to the iodoso chloride so formed and the oxidation was completed by passing in more chlorine. In all cases the iodoxy compound was obtained, and in many of them the yield was quantitative. Willgerodt regarded the oxidation of the iodoso chloride with bleaching powder or sodium hypochlorite solution to be a very good method:

$$C_6H_5ICl_2 + 2NaOCl \rightarrow C_6H_5IO_2 + 2NaCl + Cl_2$$

$$C_6H_5ICl_2 + 4HOCl \rightarrow C_6H_5IO_2 + 3Cl_2 + 2H_2O$$

$$C_6H_5IO + HOCl \rightarrow C_6H_5IO_2 + HCl$$

Formo and Johnson (17) have given directions for the preparation of iodoxyben-
zene in an 87 to 92 per cent yield, by the sodium hypochlorite oxidation of
phenyliodoso chloride. Ortoleva (54) prepared iodoxybenzene by oxidizing
phenyl iodide in aqueous pyridine with chlorine.

Iodoxy compounds have also been prepared by the direct oxidation of the
organic iodide by means of Caro's acid (3):

$$C_6H_5I + 2H_2SO_5 \rightarrow C_6H_5IO_2 + 2H_2SO_4$$
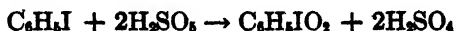
In this way phenyl iodide and o-, m-, and p-iodotoluenes were oxidized to the
corresponding iodoxy compounds. Masson and coworkers (46) used Caro's
acid and carried out the quantitative oxidation of phenyl iodide to iodoxybenzene.
They found that the iodoso compound was an intermediate product. An
excess of Caro's acid was therefore used and the materials were ground once or
twice during the operation. Böeseken and Schneider (5, 6) used perbenzoic
acid in chloroform as the oxidizing agent and thus obtained the o-diiodoxybenzene
and diiodoxyethylene from the corresponding diiodo compounds.

D. Iodonium compounds

Hartmann and Meyer (25) discovered the iodonium compounds when they
added concentrated sulfuric acid to iodosobenzene and so obtained p-iodophenyl
phenyliodonium bisulfate:

$$2C_6H_5IO + H_2SO_4 \rightarrow (C_6H_4I)(C_6H_5)I \cdot HSO_4 + H_2O + O$$
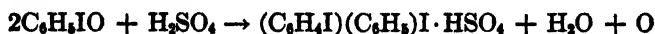
They showed that the oxygen in the above equation did not survive in any
oxidizing agent, and that it was not evolved as such; but they did not pursue
the point further, remarking "offenbar wird der Sauerstoff zur Oxydation eines
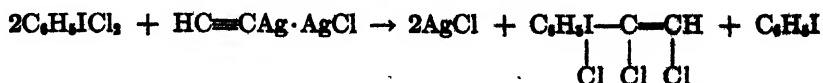kleinen Theiles der Substanz verbraucht."

The same workers (26) prepared diphenyliodonium hydroxide by shaking
equivalent quantities of iodosobenzene and iodoxybenzene with water and
silver oxide:

$$C_6H_5IO + C_6H_5IO_2 + AgOH \rightarrow (C_6H_5)_2IOH + AgIO_3$$

The filtrate from the reaction mixture contained the free base and its iodate,
and on reduction of the iodate with sulfur dioxide the iodonium iodide was
precipitated. Lucas and Kennedy (35) have prepared diphenyliodonium iodide
in a 70 to 72 per cent yield by the action of iodosobenzene on iodoxybenzene in
the presence of sodium hydroxide. The filtrate from the reaction mixture
afforded diphenyliodonium iodide on treatment with aqueous potassium iodide.
Similarly, mixed diaryliodonium compounds, such as the phenyl-p-anisylio-
donium halides (59), have been made. Lucas and coworkers (39) found that
silver oxide acts catalytically in the formation of di-o-tolyliodonium iodate from
o-iodosotoluene and o-iodoxytoluene.

The double salt of diphenyliodonium chloride and mercuric chloride has been
made by agitating a mixture of phenyliodoso chloride and mercury diphenyl
with water and finally heating to the boiling point (83, 84). Mercury diethyl

was substituted for mercury diphenyl in the hope of obtaining a phenylethyliodonium chloride, but this was not realized, the products of the reaction being ethyl chloride, phenyl iodide, and either ethylmercuric chloride or mercuric chloride. Aliphatic and mixed aliphatic–aromatic iodonium compounds (80, 90, 92, 93, 94, 95, 96) have been made by the action of the iodoso dichloride on the compound of silver chloride and silver acetylide:

$$2C_6H_5ICl_2 + HC\equiv CAg\cdot AgCl \rightarrow 2AgCl + C_6H_5I-C\equiv CH + C_6H_5I$$
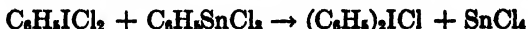$$\underset{Cl}{|}\ \underset{Cl}{|}\ \underset{Cl}{|}$$

Hepworth (29) examined the action of various Grignard reagents on iodoso and iodoso chloride compounds. He found that small quantities of diphenyliodonium and phenyl-p-tolyliodonium bases were formed by the action of phenylmagnesium bromide on the corresponding iodosochloride and iodoso compounds. There were no indications of the formation of mixed aliphatic aromatic iodonium bases by the action of alkylmagnesium halides on the same compounds.

Freĭdlina and Nesmeyanov (19) have reported the preparation of diaryliodonium salts in quantitative yields by the action of aromatic organometallic compounds of tin on iodine trichloride in dilute hydrochloric acid:

$$ICl_3 + 2C_6H_5SnCl_3 \rightarrow (C_6H_5)_2ICl + 2SnCl_4$$
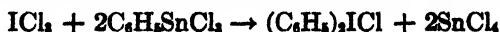
Similarly, they found that phenyliodoso chloride could be arylated:

$$C_6H_5ICl_2 + C_6H_5SnCl_3 \rightarrow (C_6H_5)_2ICl + SnCl_4$$

They also reported that diphenylmercury reacted with iodine trichloride to give the double salt of diphenyliodonium chloride and mercuric chloride. Freĭdlina and Nesmeyanov considered this method of synthesizing iodonium salts to have the advantage of simplicity and rapidity, as compared with other methods described in the literature.

Iodic acid as iodine pentoxide in suitable concentrations of sulfuric acid has been found by Masson and Race (43, 45) to attack benzene and its derivatives, with o,p-directing substituents which are not too highly activating (CH₃, Cl, Br, I), to give iodonium compounds in high yields:

$$HIO_3 + 2RH + H_2SO_4 \rightarrow R_2I\cdot HSO_4 + 2H_2O + O$$

In these particular cases it was the simplest method for preparing the iodonium compounds. The linkage between the aromatic nucleus and the iodine of the iodonium radical was always exclusively in the para position to the methyl or halogen substituent. Incidentally, this reaction furnishes a quick and delicate test for aromatic hydrocarbons in paraffins.

With anisole and other highly reactive benzene derivatives it was difficult to obtain more than traces of an iodonium product, and when the substituent was m-directing, scarcely any reaction was observed. As in nitrations, the practical success of the reaction depended upon the proper degree of hydration of the sulfuric acid and upon keeping the temperature from rising. For instance, with benzene the concentration of the acid was not weaker than $H_2SO_4:2H_2O$ and did

not exceed $H_2SO_4 : 1.2H_2O$, and the temperature was kept below 10°C., preferably at 0°C.

Along with the iodonium compound, Masson and Race found an iodine-free reducing agent, which they considered to be an open-chain unsaturated acid and 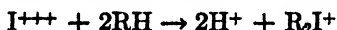a product of the oxidation of part of the organic reagent. The above equation indicated that one-third of the initial oxygen atoms was unaccounted for. It was found that in the case of chlorobenzene the missing oxygen had broken the aromatic ring in 15 per cent of the organic reagent to form a chlorinated unsaturated fatty acid. Another byproduct was the iodo derivative of the aromatic reagent. This product could be largely suppressed by using the proper working conditions.

Evidence was given that the mechanism of the process consisted of a primary deoxidation of the iodic acid to the iodous stage (HIO_2) by a fraction of the aromatic reagent, which was thereby converted into the open-chain unstaurated substance. This was followed by the direct action of the iodous acid on the organic compound to give the diaryliodonium radical:

$$2RH + OIOH \rightarrow R_2IOH + H_2\overset{.}{O}$$
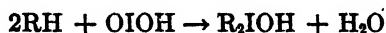
From an ionic standpoint the reaction was:

$$I^{+++} + 2RH \rightarrow 2H^+ + R_2I^+$$

or, alternatively,

$$IO^+ + 2RH \rightarrow H_2O + R_2I^+$$
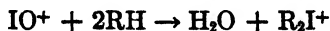
Masson and Race stated that the purpose of the sulfuric acid was to stabilize the iodous acid as an iodous sulfate and so the sulfuric acid prevented further reduction of the iodous compound by the organic reagent.

Mascarelli (41) prepared a number of iodonium bases and salts containing the iodonium iodine in a pentaatomic heterocyclic nucleus. He discovered that when 2,2'-diiodosobiphenyl or the tetrachloride was kept in water for some months the aqueous solution when treated with sulfur dioxide afforded diphenyleneiodonium iodide:
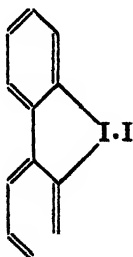
Searle and Adams (62), following the procedure of Mascarelli and Benati (42), diazotized 2,2'-diamino-4,4'-dicarboethoxybiphenyl, treated the resulting

solution with sodium iodide, and so obtained a good yield of 4,4'-dicarbæthoxy-diphenyleneiodonium iodide:

$$COOC_2H_5$$

I.I

$$COOC_2H_5$$
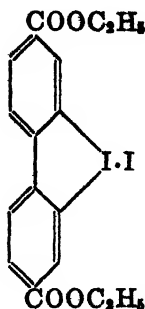
Nesmeyanov (52) has prepared the double salts of phenyldiazonium iodide and mercuric iodide and has reported the formation of small yields of diphenyliodonium salts by the decomposition of these double salts.

III. PROPERTIES OF THE COMPOUNDS OF POLYVALENT IODINE

A. *Iodoso compounds*

The iodoso compounds function as oxidizing agents and ordinarily are reduced practically irreversibly. In this respect they resemble the hypoiodites. They are quantitatively reduced to iodo compounds in aqueous acid by added iodides, and the free iodine can be titrated:

$$C_6H_5IO + 2HI \rightarrow C_6H_5I + I_2 + H_2O$$

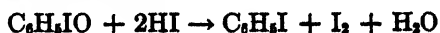This was Willgerodt's method for the estimation or iodoso compounds, and it was confirmed by Victor Meyer. Iodoso compounds can be determined in the presence of iodoxy compounds by iodide reduction at room temperature in water saturated with borax, the iodoso compound alone being attacked even during 24 hr. (38, 46).

Aryliodoso compounds readily oxidize mercaptans. Hellerman, Chinard, and Ramsdell (28) have used this as a basis for a method of some precision for the estimation of cysteine, using standard o-iodosobenzoate:

$$2\text{-OOCCH(NH}_3^+)\text{CH}_2\text{SH} + C_6H_4(\text{COO}^-)\text{IO} \rightarrow$$
$$\begin{matrix} \text{-OOCCH(NH}_3^+)\text{CH}_2\text{S} \\ | \\ \text{-OOCCH(NH}_3^+)\text{CH}_2\text{S} \end{matrix} + IC_6H_4\text{COO}^- + H_2O$$
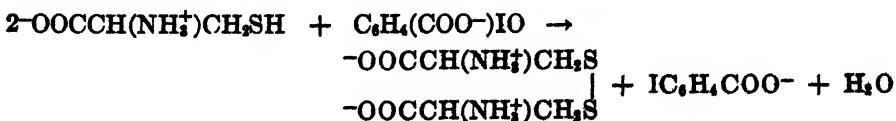
In addition, they have worked out the preparative details for the oxidation of cysteine to cystine by the o-iodosobenzoate ion. They also found that o-iodoso-benzoate as an oxidizing agent has advantages over porphyrindine and in common with porphyrindine may be used in the estimation of 0.001 N ascorbic acid.

Iodoso compounds undergo self-oxidation and reduction (77), and they afford iodonium compounds when shaken with iodoxy compounds in the presence of

wet silver oxide (26). Masson and coworkers (46) have explained these reactions as dipole additions:

$$
\begin{array}{ccc}
R-\overset{+}{I}-\overset{-}{O} & R-I \rightarrow O & R-I\rightarrow O \\[2pt]
\overset{-}{O}-\overset{+}{I}-R & \overset{\uparrow}{O} \overset{+}{\leftarrow} I-R & \overset{\parallel}{O} \ \ I-R \\[6pt]
R-\overset{+}{I} \rightarrow \overset{-}{O} & R-\overset{+}{I}-\overset{-}{O} & \\[2pt]
\overset{-}{R}-\overset{+}{IO_2} & R \ \ IO_2 &
\end{array}
$$
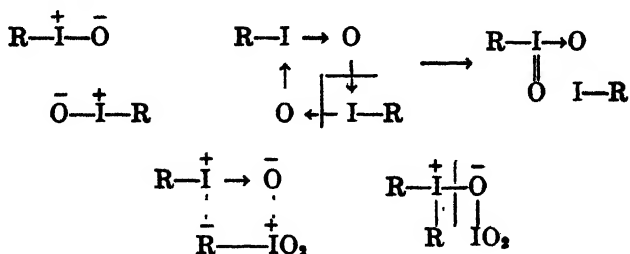
Johnson (30) has explained the same reactions on the assumption that iodine in the link between iodine and the aryl group is capable of holding temporarily a decet of electrons but shows a strong tendency to revert to an octet:

$$
2R-IO \ \rightarrow \ R-\overset{\overset{\displaystyle\bar{O}}{|}}{I} \ \leftarrow \ O-\overset{+}{I}-R \ \rightarrow \ R-\overset{\overset{\displaystyle\bar{O}}{|}}{I}-\bar{O} + R-I
$$

$$
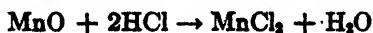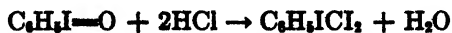R-IO_2 + R-IO \ \rightarrow \ R-\overset{+}{I}-O-\overset{\overset{\displaystyle O}{\parallel}}{\underset{\underset{\displaystyle R}{|}}{I}}-\bar{O} \xrightarrow[\text{shift}]{\alpha,\gamma-} [R-I-R]^+[IO_3]^-
$$
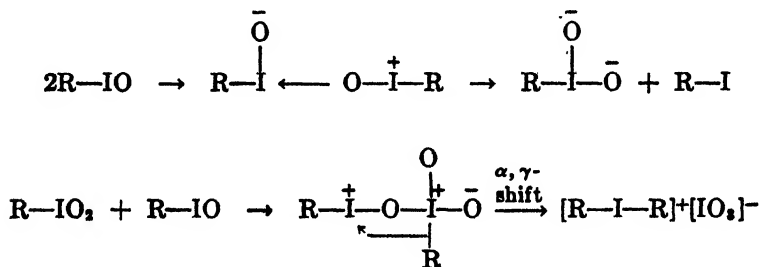
Under suitable conditions iodoso compounds are oxidized to iodoxy compounds. With iodosobenzene this is brought about by heating at 90–100°C., or more conveniently by boiling with water (75). Oxidation of iodoso compounds is also effected readily by means of aqueous hypochlorite (81).

Iodoso compounds behave in general as the anhydrides of the hypothetical diacid base RI(OH)₂. An organic iodoso chloride is therefore the hydrochloric acid salt of the weak diacid base RI(OH)₂, of which other salts such as the acetate are also known. The preparation of iodoso salts from iodoso compounds brings out the analogy which exists between the iodoso compounds and such basic oxides as manganous oxide and lead monoxide:

$$C_6H_5I=O + 2HCl \rightarrow C_6H_5ICl_2 + H_2O$$

$$MnO + 2HCl \rightarrow MnCl_2 + H_2O$$

$$PbO + 2HCl \rightarrow PbCl_2 + H_2O$$

Tscherniac (69) found that phthalimide was readily transformed into anthranilic acid when shaken with alkali and iodosobenzene. The iodosobenzene in this case plays the part of the alkali hypochlorite in the ordinary Hofmann transformation of acid amides into amines.

In general, the iodoso compounds are yellow amorphous solids and explode or decompose with a puff on heating.

B. Iodoso salts

The iodoso salts, like the iodoso compounds, are oxidizing agents and liberate iodine from potassium iodide. Criegee and Beucker (8) have used aryliodoso acetates as oxidizing agents on unsaturated compounds such as anethole and have determined the reaction velocities at 20°C. The bimolecular coefficients decreased with time in all cases and were all of the same order, as was that for lead tetraacetate. Cyclopentadiene reacted with phenyliodoso acetate, m-4-xylyliodoso acetate, and p-nitrophenyliodoso acetate to give 52 to 73 per cent of diacetoxycyclopentenes. There was evidence that some 1,4-addition of two acetate groups to the conjugated system had occurred, which was also the case with lead tetraacetate. The fission of α,β-glycols by phenyliodoso acetate was found to occur much more slowly than with lead tetraacetate, and the reaction probably proceeded through a cyclic intermediate. Iodoso chlorides were found not capable of splitting glycols, and free iodosobenzene did not lend itself to this reaction because of its insolubility. In some respects the aryliodoso acetates were found to be better oxidizing agents than lead tetraacetate, especially from the standpoint of non-formation of inorganic products.
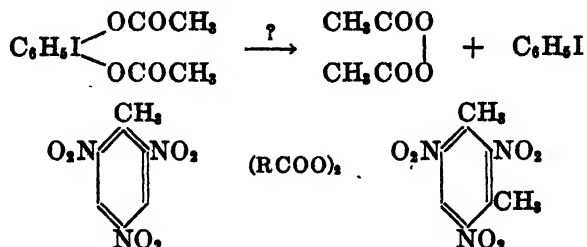
Aryliodoso chlorides decompose, on heating, usually into the iodo compound and chlorine. There is also the migration of chlorine to ring carbon with the formation of hydrogen chloride and a chlorine substitution compound. Phenyliodoso chloride, for example, decomposes at 120–121°C., giving up chlorine and hydrogen chloride. This property has been used in the characterization of aryl iodides (58). Leicester and Bergstrom (33), working on the thermal decomposition of triphenylselenonium iodide, characterized iodobenzene by its conversion into phenyliodoso chloride and further checked by a mixed melting point with a known sample of phenyliodoso chloride.

At low temperatures methyl iodide forms a solid chloride, CH_3ICl_2, which decomposes into methyl chloride and iodine monochloride at $-30°C$. Johnson (30) has expressed these reactions in the following way:

$$CH_3I + Cl_2 \xrightarrow{-80°C.} CH_3I \leftarrow ClCl \xrightarrow{\alpha,\gamma\text{-shift}} ICl + CH_3Cl$$
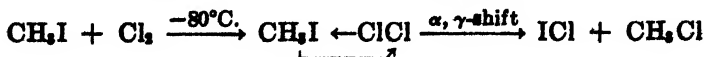
Fieser and coworkers (12, 13, 15) have carried out some very interesting work on the alkylation of α-naphthoquinones and aromatic nitro compounds with tetravalent lead esters, such as lead tetraacetate. They have shown that with the latter reagent, 2-methyl-1,4-naphthoquinone, for example, can be converted into 2,3-dimethyl-1,4-naphthoquinone in yields as high as 50 per cent. By this method trinitrotoluene has been converted in yields as high as 32 per cent into trinitro-m-xylene, which appears to be an end product. Prompted by this work, the author of this review (58) has carried out some initial exploratory work on the behavior of phenyliodoso acetate towards compounds such as trinitrotoluene. It has been found that phenyliodoso acetate, like lead tetraacetate,

behaves as a methylating agent, although the yield does not seem to be as high. It might be supposed that phenyliodoso acetate, like lead tetraacetate, undergoes decomposition to the acyl peroxide, which is the alkylating agent:

$$C_6H_5I{\Large\langle}\begin{matrix}OCOCH_3\\OCOCH_3\end{matrix} \xrightarrow{\;?\;} \begin{matrix}CH_3COO\\ |\\ CH_3COO\end{matrix} + C_6H_5I$$

Lead tetraacetate is also known to be an acetoxylating agent. Reactive hydrocarbons, such as acenaphthene (11), anthracene (49), and 3,4-benzpyrene (14), undergo acetoxylation at temperatures below that at which the methylative action of lead tetraacetate becomes operative. Similarly, one might expect phenyliodoso acetate to function as an acetoxylating agent. This phase is now being investigated by the author.

Garvey, Halley, and Allen (20) have used phenyliodoso chloride as a chlorinating agent and have found that it gives the same products as chlorine, but that it is milder in its action. Unsaturated compounds, such as benzalacetophenone, trans-benzoylethylene, and 2-pentene, were found to add chlorine when heated with phenyliodoso chloride in ethylene chloride. Cinnamic acid and benzene did not react. Similarly, p-tolyliodoso fluoride was used as a fluorinating agent. This compound in chloroform reacted with simple olefins and stilbene to give mixtures. Rubber gave a white amorphous powder, apparently a monofluoro derivative. Indications were that the iodoso fluoride acted as a direct fluorinating agent at the double bond and that the resulting olefin fluoride decomposed with the evolution of hydrogen fluoride.

p-Tolyliodoso fluoride also reacted with certain aromatic polynuclear hydrocarbons and ketones to give two types of products, one formed by the substitution of hydrogen by fluorine and the other by a coupling reaction. Acenaphthene gave diacenaphthene. Anthrone formed dianthrone. Pyrone gave a monofluoropyrene and a bipyrenyl. Anthracene and benzanthrone gave only monofluoro derivatives.

Bockemüller (4), in examining the behavior of aryliodoso fluorides on some organic compounds, found that α,α-diphenylethylene did not react in chloroform or nitrobenzene at ordinary temperatures. However, in the presence of a little anhydrous hydrogen fluoride or silicon tetrafluoride the formation of α,β-difluoro-α,α-diphenylethane occurred in 60 per cent yield, accompanied by the production of oily material which evolved hydrogen fluoride when distilled. α,α-Diphenyl-β-methylethylene was fluorinated with relative ease to α,α-diphenyl-β-methyl-α,β-difluoroethane in 77 per cent yield. Stilbene, α-methylstilbene, anthracene, and phenanthrene gave fluorine-containing

compounds from which no definite products could be isolated. Diethylaniline was fluorinated to p-fluorodiethylaniline and dehydrogenated to tetraethylbenzidine.

The property of aryliodoso chlorides of liberating iodine from metal iodides and of acting as a chlorinating agent has been extended by Neu (53) to thiocyanates and to the chlorination of a number of organic compounds. Thus, phenyliodoso chloride with lead thiocyanate in acetic acid, methylene chloride, chloroform, carbon tetrachloride, and ethyl acetate formed solutions which gave the reactions of free thiocyanogen and with which organic compounds could be thiocyanated. For thiocyanation purposes phenyliodoso chloride was added, with cooling, to a suspension of 1.5 moles of dry lead thiocyanate in the organic solvent, shaken until the crystals or the yellow color of phenyliodoso chloride disappeared, and then filtered through a folded filter dried at 105°C. Atmospheric moisture was carefully excluded. Such a solution, added in small portions to aniline in chloroform and allowed to stand overnight, gave a 50 per cent yield of 1-amino-4-thiocyanobenzene. Other compounds, such as phenol, dimethylaniline, o-aminophenol, m-aminophenol, catechol, benzidine, p-phenetidine, thymol, anthranilic acid, β-naphthol, and β-naphthylamine, were similarly thiocyanated. Repeated attempts to thiocyanate p-aminophenol and salicylic acid were unsuccessful. Phenol, acetanilide, salicylic acid, and β-naphthol were readily chlorinated by phenyliodoso chloride in suitable solvents. Phenyliodoso acetate oxidized aniline to azobenzene with good yields and p-phenetidine gave a substance with the properties of a phenazine.

LeFèvre and Markham (32), in accord with Hepworth (29), found that no chlorobenzene was formed when phenyliodoso chloride reacted with phenylmagnesium bromide. Instead, there was produced mainly phenyl iodide and biphenyl. Chlorination of the ether also occurred, which was interesting, since phenyliodoso chloride and ether have been found not to react in the absence of the Grignard reagent.

Mel'nikov (48) isolated phenyl chloride, phenyl bromide, phenyl iodide, biphenyl, and diphenyliodonium chloride from the reaction product of phenyliodoso chloride and phenylmagnesium chloride. The reaction products from p-tolyliodoso chloride and phenylmagnesium chloride were phenyl chloride, phenyl bromide, p-tolylphenyl, and phenyl-p-tolyliodonium chloride.

Phenyliodoso chloride has been used as a nitridizing agent (10) in liquid ammonia. It reacted with ammonia in the liquid or gaseous state to give nitrogen, phenyl iodide, and ammonium chloride. In chloroform phenyliodoso chloride converted hydrazobenzene into a mixture of azobenzene and benzidine hydrochloride. In liquid ammonia it acted on hydrazobenzene according to the equation:

$$C_6H_5ICl_2 + C_6H_5NNC_6H_5 + 2NH_3 \rightarrow C_6H_5I + C_6H_5N=NC_6H_5 + 2NH_4Cl$$
$$HH$$
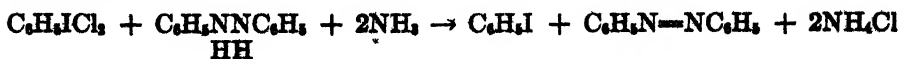
On the supposition that iodoso compounds are like nitroso compounds, Pieroni (56) has examined the behavior of phenyliodoso chloride on aniline. When

these two compounds were mixed in pyridine as the solvent, a deep brown color
was produced and heat was evolved. The product was $C_6H_5NCl(C_6H_5ICl)_3$.

$$3C_6H_5ICl_2 + C_6H_5NH_2 \rightarrow 2HCl + C_6H_5NCl(C_6H_5ICl)_3$$
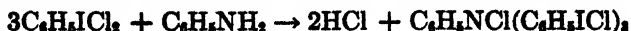
Sidgwick and Barkworth (63) determined the parachor of phenyliodoso
propionate in order to find out the effect of an increase in valence on the para-
chor. The experimental value was found to be 583.5. The calculated value is
600.8, which gave a parachor defect of 17.3.

C. Iodoxy compounds

The iodoxy compounds, like the iodoso compounds and iodoso salts, are oxidiz-
ing agents and are comparable to iodates. They are quantitatively reduced
in aqueous acid by added iodides, with the liberation of iodine which can be
titrated:

$$C_6H_5IO_2 + 4HI \rightarrow 2H_2O + C_6H_5I + 2I_2$$

Masson, Race, and Pounder (46) found that in the estimation of nitroiodoxy-
benzene, where the reduction product is a solid, the addition of alcohol-free
chloroform near the end of the titration with thiosulfate ensured a sharp end
point by releasing mechanically engaged iodine.

The above workers called attention to two simple properties of iodoxybenzene:
viz., although it can be heated to 230°C., it neither melts nor vaporizes, and while
it is slightly soluble in water, it is still less so in chemically inert solvents. These
properties are shared by all iodoxy compounds. According to Masson and
coworkers, the reason for this is not polymerization, because iodoxybenzene is
monomeric in aqueous solution. The reason is probably due to internal polarity
which is not ionic in nature, i.e., iodoxybenzene is not diphenyliodonium
periodate. The high polarity must therefore have its source within the iodoxy
group.

Willgerodt considered iodoxybenzene to be a neutral compound (88), and
many textbooks have described the iodoxy compounds as having no basic
properties. Masson (46) found iodoxybenzene to be amphoteric and that it
afforded the following salts with acids: $C_6H_5IO_2 \cdot H_2SO_4$, m.p. 127°C., and the
perchlorate, which was highly explosive. Iodoxybenzene is a stronger base
than nitrobenzene, for, according to Masson, $C_6H_5IO_2 \cdot H_2SO_4$ is formed in an
acid sufficiently dilute to hydrolyze $C_6H_5NO_2 \cdot H_2SO_4$ completely. Weinland
and Stille (74) made the compound $C_6H_5IOF_2$ by treating iodoxybenzene with
hot concentrated hydrofluoric acid:

$$C_6H_5IO_2 + 2HF \rightarrow H_2O + C_6H_5IOF_2$$

This reaction was considered by Masson and his coworkers to be a second stage
in the reaction which gave them $C_6H_5IO_2 \cdot H_2SO_4$, a molecule of water having been

eliminated, while hydrochloric acid went still further and was oxidized, a second molecule of water having been formed (78).

The formation of salts from iodoxy compounds and alkalies has been demonstrated by a combination of rapid measurements of solubility, conductivity, and freezing point (46). The reaction is

$$C_6H_5IO_2 + OH^- \rightleftarrows C_6H_5IO_2 \cdot \overline{O}H$$
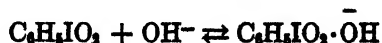
Iodoxybenzene behaves as if it were a monobasic acid with a dissociation constant of the order of 1×10^{-11}. The slight conductivity measured for pure aqueous iodoxybenzene gives an apparent $K = 10^{-10.4}$. Masson has called the salts of iodoxy compounds and bases phenyliodoxylates. They change very rapidly irreversibly and quantitatively soon after their formation in cold alkali, according to the equation:

$$2C_6H_5IO_2^-H \rightarrow (C_6H_5)_2IO \cdot OH + IO_3^- + OH^-$$

The new compound, diphenyliodyl hydroxide, is amphoteric and is a strong oxidizing agent, being readily reduced by sulfur dioxide, hydrogen peroxide, hydrogen iodide, and dilute hydrochloric acid to form salts of diphenyliodonium hydroxide:

$$(C_6H_5)_2IO \cdot OH + 3HI \rightarrow (C_6H_5)_2I \cdot I + I_2 + 2H_2O$$
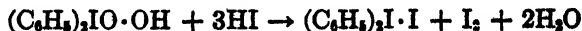
This is the origin of the iodonium salts obtainable from alkaline solutions containing iodoxy compounds on treatment with any of the reagents just mentioned, and it explains the qualitative results obtained by Willgerodt (82) in the action of iodoxybenzene with barium hydroxide or with boiling potassium iodide. With the latter compound the alkali needed is formed according to the equation:

$$C_6H_5IO_2 + 2KI + H_2O \rightarrow C_6H_5I + I_2 + 2KOH$$
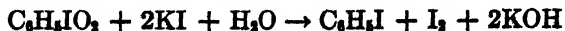
The opinion expressed by Willgerodt as to the possible formation of "jodonate" by iodoxybenzene and barium hydroxide, although contradicted in his monograph, has definitely been justified by Masson and coworkers.

Considerable work has been done on the alkaline hydrolysis of iodoxy compounds, and all of the compounds examined yield the iodoxy group as iodate (24, 40, 46, 65, 71, 72, 73). With dilute sodium hydroxide at 15–20°C., p-iodoxynitrobenzene has been found to give the expected p-nitrophenol in only subordinate amounts. The main reaction was the replacement of the iodoxy group by hydrogen, with the formation of nitrobenzene and sodium iodate. With silver oxide in water at 15–20°C., silver iodate was formed in 98.8 per cent yield. The prolonged action of cold dilute alkali upon iodoxybenzene or the rapid action of $1 N$ alkali at 100°C. resulted in the formation of benzene and the alkali iodate. According to Masson, the reaction of iodoxybenzene, which is different from other iodoxy compounds in that it contains no activating sub-

stituents, indicates that the iodoxy group is "labile" in alkali and that its iodine is positive towards the organic residue. This fits in with the fact shown by Hartmann and V. Meyer (24) that o-iodoxybenzoic acid is a strong acid. It is highly probable that the alkaline hydrolysis of iodoxy compounds proceeds by way of the formation and subsequent decomposition of iodyl compounds. Diphenyliodyl acetate, when it is boiled with 1 N sodium hydroxide, affords benzene and iodate accompanied by less simple reactions (46).

Vorländer (70) found that iodoxybenzene was attacked by nitric acid only with great difficulty, indicating that the iodine atom of the iodoxy group is positive in character. By guarding against the presence of nitrous acid, which reduces the iodoxy to the iodo compound, it has been possible to carry out the mononitration of iodoxybenzene to an extent of not less than 98.6 per cent and the product is about 99.5 per cent the meta compound (46). This puts the iodoxy group on a par with that of free aromatic ammonium and similar cations and is more evidence in favor of the strongly dipolar character of the iodoxy group.

Because of their explosive properties, iodoxy compounds should be heated with extreme care. Iodoxybenzene is known to explode by impact. Morrison and Legge (51) have done work on the impact sensitivity of iodoxybenzene. They have found that it explodes on an anvil when struck with a hammer and that it undergoes decomposition when hit by a 500-g. weight falling through a distance of 100 cm. It was also found that its power in the sand-crushing test was very low. Iodoxybenzene deflagrates when touched with a hot wire.

Grossman (21) has described an iodoxy–iodosobenzene electrode for the determination of hydrogen- and hydroxyl-ion concentrations. It is analogous to the quinhydrone electrode and the underlying reaction is:

$$C_6H_5IO + 2OH^- + 2e \rightleftarrows C_6H_5IO_2 + H_2O$$

D. Iodonium compounds

The iodonium bases, such as diphenyliodonium hydroxide, are strong bases and form stable salts when neutralized with acids. In this respect they are analogous to the quaternary ammonium bases and the tertiary sulfonium bases.

The iodonium compounds are decomposed by heat, and in this respect they again resemble other onium compounds. For example, diphenyliodonium iodide on heating decomposes to give iodobenzene:

$$(C_6H_5)_2I \cdot I \rightarrow 2C_6H_5I$$
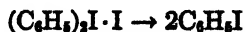
The decomposition temperature of an iodonium salt depends upon the nature of the anion as well as the cation. Keeping the positive ion the same, we find roughly that the decomposition temperature of an iodonium salt varies with the electronegativity of the negative ion. For instance, di-o-tolyliodonium bromide decomposes at 178°C., the iodide at 155°C., and the sulfide at room temperature.

In the opinion of the reviewer this is reminiscent of the cleavage of thiamin by sodium bisulfite (98), and the cleavage of benzyldimethylphenylammonium chloride by sodium hydrosulfide, sodium sulfide, sodium thiosulfate, sodium bisulfite, and sodium sulfite (64).

Searle and Adams (62) heated 4,4'-dicarboethoxydiphenyleneiodonium iodide for 5 min. at 218°C. and obtained 2,2'-diiodo-4,4'-dicarboethoxybiphenyl:

$$\text{COOC}_2\text{H}_5 \qquad\qquad \text{COOC}_2\text{H}_5$$

I·I

$$\text{COOC}_2\text{H}_5 \qquad\qquad \text{COOC}_2\text{H}_5$$
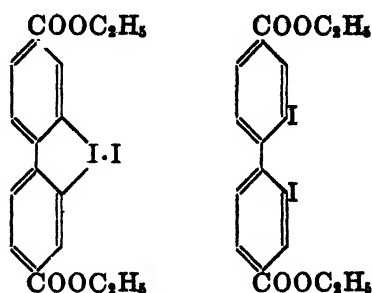
Lucas, Kennedy, and Wilmot (39) have worked with di-*o*-tolyliodonium iodide, which decomposes at 155°C. in a reaction which proceeds *via* the mechanism of an intermediate positively charged ion. There are, according to Lucas and coworkers, two possible mechanisms by which the decomposition might take place: (*a*) migration of the iodide iodine to one of the benzene rings in a position ortho or para to the C—I bond, followed by the scission of the C—I bond; (*b*) the scission of a C—I bond, followed by the attachment of the resulting positive organic ion to the negative iodide ion. The two mechanisms are pictured below:

(*a*) *Migration first:*

I

CH₃ I CH₃   CH₃   CH₃

+

I   III   IV

↓

H

CH₃ I CH₃   CH₃   CH₃

+

II   V   VI

(b) *Scission first:*

CH₃ I CH₃   + I   CH₃   +   CH₃   + I⁻

VII   VIII   IX

↓   ↓

CH₃ CH₃   + I₂   CH₃   +   CH₃

XI   X
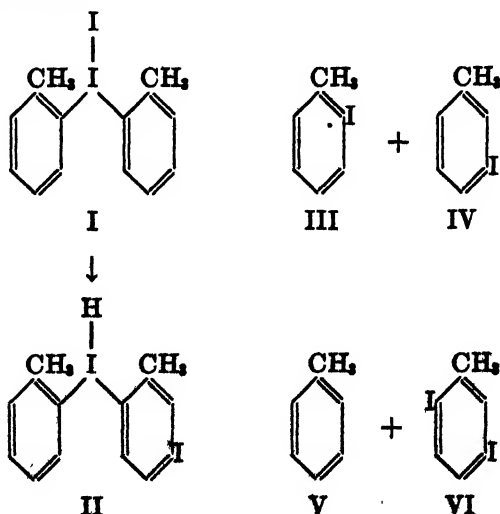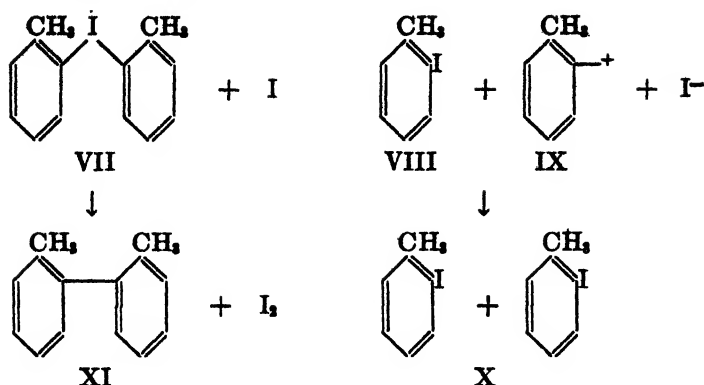
If the two iodine atoms are held together by a covalent bond (I), the migration of iodine to an ortho or para position on the benzene ring is quite plausible. If migration is the first step, then scission of a C—I bond in the hypothetical intermediate (II) should lead to the formation of a mixture of equal parts of o-iodotoluene and m-iodotoluene (IV), or a mixture of equal parts of toluene (V) and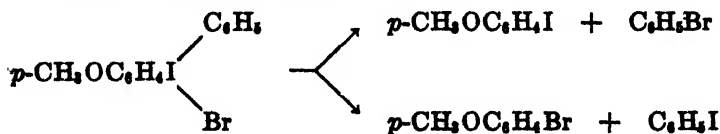 2,5-diiodotoluene (VI), or a mixture of the four compounds. However, if the original is ionized, then the iodide ion would not migrate to the ring. A mechanism might be the formation (*1*) of equal amounts of o-iodotoluene (VIII) and positive o-tolyl ion (IX) by the breakage of a C—I bond and (*2*) the combination of this ion with the negative iodide ion to form a second molecule of o-iodotoluene (X). This would afford pure o-iodotoluene. If both C—I bonds should break simultaneously, the products would be o,o'-bitolyl (XI) and iodine. Actually, Lucas and his coworkers found that the decomposition resulted in the formation of pure o-iodotoluene. This indicated that the iodonium ion split into o-iodotoluene and the positive o-tolyl ion by a scission of the C—I bond. The o-tolyl ion and the iodide ion then produced another molecule of o-iodotoluene.

The decomposition of compounds such as phenyl-p-anisyliodonium chloride, bromide, and iodide has been examined (59). In the case of phenyl-p-anisyliodonium bromide the decomposition may lead to p-iodoanisole and bromobenzene or to p-bromoanisole and iodobenzene:

$$p\text{-}CH_3OC_6H_4I \Big\langle \begin{matrix} C_6H_5 \\ Br \end{matrix} \quad \begin{matrix} \nearrow & p\text{-}CH_3OC_6H_4I \ + \ C_6H_5Br \\ \searrow & p\text{-}CH_3OC_6H_4Br \ + \ C_6H_5I \end{matrix}$$

Actually, at least 87 per cent and possibly more of the decomposition followed the first reaction scheme. Thus the decomposition occurred in such a way that the more electronegative radical (p-anisyl) remained attached to the iodine atom.

Sandin, McClure, and Irwin (60) have found that diphenyliodonium chloride

and di-*p*-tolyiodonium chloride react with mercury in boiling *n*-propyl alcohol to produce phenylmercuric chloride and *p*-tolylmercuric chloride. With tellurium the same iodonium salts gave diphenyltellurium and di-*p*-tolyltellurium. Diphenyliodonium sulfide decomposed at room temperature in the presence of tellurium and antimony to give diphenyltellurium and triphenylstibinic sulfide.

In view of the results obtained, Sandin and coworkers assume that in the decomposition of an iodonium salt part of it at least can decompose by way of a non-ionic mechanism. The assumption is made that in the iodonium salt the central iodine atom is able, by expanding its valence shell, to act as an acceptor for the chloride or sulfide ion. Subsequent transformations of this complex result from the tendency of the central atom to revert to an octet. The following is suggested as a probable course of the reaction:

$$(C_6H_5)_2I^+Cl^- \rightarrow (C_6H_5)_2I \leftarrow Cl \rightarrow C_6H_5I + C_6H_5 \cdot + \cdot Cl$$
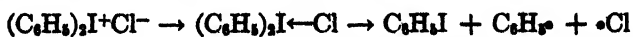
Professor H. J. Lucas of the California Institute of Technology has kindly drawn attention to the important rôle played by the metal in the decomposition reactions. He suggests the possibility of an intermediate, undissociated complex which decomposes at a lower temperature than the salt would otherwise. Such a reaction mechanism would not necessarily involve the formation of free radicals. On this basis also, the decomposition with and without a metal would not necessarily have to proceed *via* similar mechanisms.

Fletcher and Hinshelwood (16) have studied the rate of decomposition of diphenyliodonium iodide in the solid state and in solution in iodobenzene. The activation energy for the reaction in the solid state was found to be 26,300 calories and that for the reaction in solution was 27,000 calories (uncorrected for change in viscosity). The decomposition in solution is probably unimolecular, as is the case for quaternary ammonium salts.

In the electrolysis of aqueous solutions of diaryliodonium hydroxide with a mercury cathode, no amalgam was formed. With the hydroxides of diphenyl-, *o*-dianisyl-, and *p*-dianisyl-iodonium, there was formed, in addition to the corresponding iodine derivatives, biphenyl, *o,o'*-bianisyl, and *p,p'*-bianisyl, respectively (102). The electrolysis of diphenyliodonium chloride in absolute ethanol with a mercury cathode has been shown to form some diphenyliodonium iodide (58).

Diphenyliodonium nitrate has been nitrated and the amount of meta nitration has been shown to be at least 82.5 per cent (7, 60, 70). This indicates the positive nature of the iodine atom towards the anion as well as both benzene nuclei. The nitration of a compound such as diphenyliodonium nitrate might be expected to be similar to the nitration of phenyltrimethylammonium nitrate, since the orienting group is —$IC_6H_5^+$. However, the iodine atom in —$I(C_6H_5)^+$ has unshared electrons and is at the same time the positive end of a dipole. On the basis of unshared electrons one might expect the formation of some ortho and para derivatives along with the meta compound. There is also another difference between phenyltrimethylammonium nitrate and diphenyliodonium nitrate to be considered. Since the positive electricity resides at the nucleus

of the charged atom, the amount of damping action arising through the passage of the effect through the successive shells of electrons belonging to the charged atom itself would be smaller for the former than for the latter compound. On this basis it might be expected that the iodonium compound would show weaker meta reactivity. The results of Challenger and Rothstein (7) showed a para nitration which varied from 14 to 20.2 per cent. The work of Sandin, McClure, and Irwin (61) indicated a minimum of 18.5 per cent of para nitration. At least 10 per cent of the rearranged reaction mixture could be isolated as *p*-iodonitrobenzene.

Copley (9) has announced a rule which relates valency to orientation. If X is the atom attached to the benzene nucleus in the compound C_6H_5Y, then the group Y which contains X is an *o*,*p*-directing group when the valence of X is equal to or less than 4, and a *m*-directing group when the valence of X is greater than or equal to 4, a transition occurring at 4. The iodonium group is cited as an exception to this rule.

Medlin (47), by means of x-ray investigations, has shown that the distance between the iodine atoms in diphenyliodonium iodide is 3.55 Å., which is compatible with an ionic and not a covalent structure. The stability against interchange of the iodine atoms in diphenyliodonium iodide has been studied. Juliusburger, Topley, and Weiss (31) crystallized this salt from ethanol and water containing sodium iodide made radioactive by neutron bombardment. The resulting solid was strongly radioactive. Diphenyliodonium hydroxide derived from it was converted to the iodide with inactive sodium iodide and was inactive. Therefore the interchange occurred with the negative iodine only. Boiling for 20 min. in ethanol and water gave no interchange. In a solution of diphenyliodonium iodide (with the negative iodine radioactive) in iodobenzene no detectable exchange took place even under conditions so extreme that considerable decomposition into iodobenzene occurred. If both the decomposition and exchange reactions involve an activated complex, it is probable that the activation energy for the decomposition is less than for the exchange.

The ionizable iodine in iodonium iodides is capable of assuming fresh combining power quite as readily as the halogen in iodobenzene. The periodide of diphenyliodonium iodide, $(C_6H_5)_2I_4$, has been made by treating diphenyliodonium iodide with a solution of iodine in ethanol, a reaction which recalls the periodides of the alkylammonium bases. There has also been described the tetrachloride, dichloride, iodochloride, dibromide, and iodobromide of diphenyliodonium iodide, the iodide and dibromide of diphenyliodonium chloride, and the diiodide and dibromide of diphenyliodonium bromide (18, 27, 91).

Iodonium compounds of the type IR′ R″ R‴ have not been separated into optically active components (55). The optical activity of diphenyliodonium tartrate has been investigated by Pribram (57) and the analogy of such salts with those of thallium has been pointed out. As the tartrate could not be obtained in the crystalline state, solutions of diphenyliodonium hydroxide and tartaric acid were mixed in equivalent proportions. The observed rotations

in solutions of the iodonium tartrate were found to be in each case greater than that of solutions containing equivalent amounts of free tartaric acid.

Masson and Race (45) have called attention to the important fact that bis-(p-chlorophenyl)iodonium hydrogen sulfate can exist as an oily form and is partly soluble in chloroform in which it undergoes fission to some extent, producing the aromatic iodo compound. With reference to these properties, Masson and Race have made the important observation that it "points to marked polarisability of the anion by the cation," and that "it seems clear that any strong interionic polarisation, the effects of which are to induce, as has been mentioned, properties tending towards those of covalent compounds, must play an important part in initiating the wholly irreversible fission which all iodonium salts undergo when they are heated, $R_2I \cdot X \rightarrow RI + RX$, wherein the hitherto anionic X becomes covalently attached to one of the radicals R."

In case the reader has been wondering if there are chloronium and bromonium compounds, his attention is called to the very interesting work of Winstein and Lucas (99) and Lucas and Gould (34). These workers have shown that a cyclic positive ethylenebromonium ion is an intermediate when (+)-*threo*-3-bromo-2-butanol is converted into *dl*-2,3-dibromobutane by the action of hydrobromic acid. They have also shown that the concept of the cyclic chloronium ion is useful in accounting for *trans*-addition of chlorine and hypochlorous acid to the 2-butenes and for the purity of the resulting dichlorides and chlorohydrins.

IV. STRUCTURES

The structure of an iodoso compound is shown best by means of an electronic formula. For example, iodosobenzene is given a structure which contains 2-covalent iodine:

$$C_6H_5 : \overset{..}{\underset{+}{I}} : \overset{..}{\underset{-}{O}} :$$
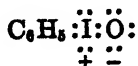
Masson, Race, and Pounder (46) have considered the structure of the iodoso group in this way, when they refer to some of the reactions of iodoso compounds as being dipole additions. However, they have said, "We do not here prejudge the question whether the iodoso group contains a double bond or a single coordinate link, or whether the former is polarised into the latter by the reagent prior to its final conversion into an electrovalency." Similarly, the iodoso salts such as phenyliodoso chloride and phenyliodoso acetate are best represented by the structures:

$$\left[C_6H_5 : \overset{..}{\underset{..}{I}} : \overset{..}{\underset{..}{Cl}} : \right]^+ \left[: \overset{..}{\underset{..}{Cl}} : \right]^- \quad \text{and} \quad [C_6H_5I(OCOCH_3)]^+ (OCOCH_3)^-$$

Johnson (30) has represented the formation of phenyliodoso chloride from iodobenzene and chlorine by the equation:

$$C_6H_5I + Cl_2 \rightarrow C_6H_5I \leftarrow ClCl \rightarrow [C_6H_5ICl]^+ Cl^-$$

He has indicated the change of phenyliodoso chloride into iodosobenzene by the following:

$$[C_6H_5ICl]^+ \xrightarrow{OH^-} \overset{\overset{\displaystyle Cl}{|}}{C_6H_5I}{\leftarrow}OH \rightarrow C_6H_5\overset{+-}{I}O + HCl$$
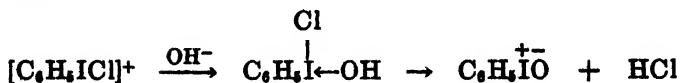
The dipole moments of phenyliodoso chloride and its derivatives have been determined by Guryanova and Syrkin (22). As a result of their work, they have considered these compounds to be mixtures of homopolar and internally ionized structures. The values of the dipole moment in excess of the vector sum are believed to be due to resonance effects.

Zappi and Degiorgi (101) studied the reaction between phenyliodoso chloride and methylmagnesium iodide in various solvents and from their results were led to the belief that phenyliodoso chloride is ionized in solution:
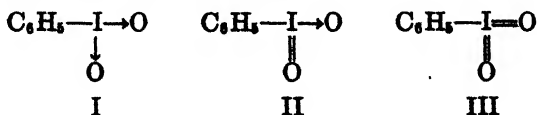
$$C_6H_5ICl_2 \rightleftarrows ClH_5ICl^+ + Cl^-$$

They provisionally assigned the structure $[C_6H_5ICl]^+Cl^-$ to phenyliodoso chloride. Later, Zappi and Cortelezzi (100) determined the molecular weight and electrical conductivity of phenyliodoso chloride in various solvents and came to the conclusion that any dissociation which occurred was molecular:

$$C_6H_5ICl_2 \rightleftarrows C_6H_5I + Cl_2$$

They decided that the ionic formula for phenyliodoso chloride should be discarded.

Askenasy and Meyer (2) ascribed the extremely feeble acidic properties of o-iodosobenzoic acid to internal-ring formation, with which view Willgerodt agreed. Solely on the basis of the polarity of the I—O group, o-iodosobenzoic acid might have been expected to be a strong acid. That o-iodosobenzoic acid yields salicylate and not benzoate when boiled with alcoholic sodium hydroxide has been explained by Masson, Race, and Pounder (46) to be due to the easy reduction of iodyl compounds by hot alcohol to iodo compounds, and to the fact that o-iodobenzoic acid is capable of alkaline hydrolysis to salicylic acid. Therefore the properties of o-iodosobenzoic acid are not in contradiction with the belief that the iodine of the iodoso group is positive in character.

Of the three structures for iodoxybenzene

$$
\begin{array}{ccc}
C_6H_5{-}I{\rightarrow}O & C_6H_5{-}I{\rightarrow}O & C_6H_5{-}I{=}O \\
\downarrow & \Vert & \Vert \\
O & O & O \\
\text{I} & \text{II} & \text{III}
\end{array}
$$

Masson, Race, and Pounder (46) prefer structure II. In this structure there is the opportunity for resonance, which would explain the greater stability of iodoxy compounds over that of the iodoso compounds. Structures I and II both indicate internal polarity, which fits in with the refractory properties of the iodoxy compounds.

Johnson (30) has used structure I, which contains 3-covalent iodine, in his equations showing the dismutation of iodoso compounds and the formation of iodonium compounds.   Electronically structure I is

$$-:\overset{\cdot\cdot}{O}:$$
$$C_6H_5+:\overset{\cdot\cdot}{I}:+\overset{\cdot\cdot}{O}:-$$
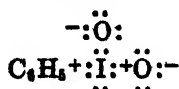
Before a final choice between these structures can be made, chemical evidence needs to be supported by data from x-ray work. Masson has pointed out the difficulty of carrying out the parachor and dipole-moment measurements.

The structure of the salt of an iodoxy compound and an acid is represented by Masson, Race, and Pounder (46) as:

$$\left(C_6H_5 - I \overset{O}{\underset{O}{\nearrow\searrow}} H \right)^\bullet \ldots \ldots X'$$
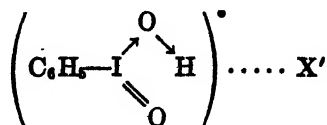
The iodoxy compound in this case plays a cationic part in which univalent hydrogen is associated with the resonance between the two oxygen linkages, the anion remaining as such.   On the other hand, the salt of an iodoxy compound and a base is shown as:

$$C_6H_5 - \overset{O}{\underset{O^-}{\overset{\parallel}{I}^+}} \ldots \ldots (OH)'$$
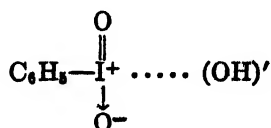
In the first type of salt, one end of the dipole $\overset{+}{I} - \overset{-}{O}$ has coördinated H; in the second case, the other end of the same dipole has combined with OH⁻, the cation of the alkali remaining as such.   Masson and coworkers say that they have no evidence to justify a supposition that in the latter type of salt (iodoxylates) the union with the OH can become covalent:

$$C_6H_5 - \overset{O}{\underset{O}{\overset{\cdot}{I}}} - O - H \left. \right\rangle '$$
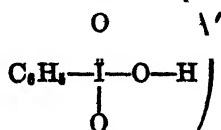
To account for the fact that the salts of the stronger acids and diphenyliodyl hydroxide seem to be less stable than the carbonate and the acetate, Masson et al. (46) have suggested for the carbonate and acetate coördinated ring structures such as:
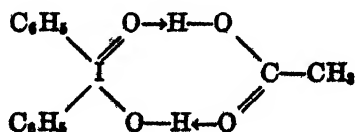
and
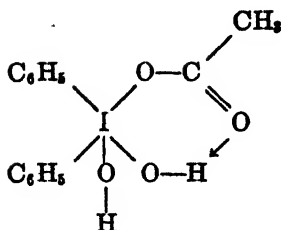
There seems to be no doubt regarding the ionic structure of the iodonium compounds (31, 47), and here again we notice the similarity between iodonium compounds and other onium compounds. Electronically the iodonium compounds are represented:

Like the iodoso compounds, they contain 2-covalent iodine.

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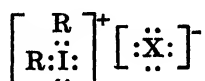(1) ARBUZOV, B. A.: J. prakt. Chem. **131**, 357 (1931).
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THE PLATINUM METALS

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CONTENTS

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I. INTRODUCTION

From 1915 to 1940 approximately eight hundred papers dealing with the inorganic and analytical chemistry of the platinum metals were published. Roughly, about 70 per cent of the number are concerned with the preparation and properties of complex compounds and with constitutional structure, and about 10 per cent with the inorganic chemistry of comparatively simple compounds. The remaining number may be classed under the subject of analytical chemistry.

The only possible logical arrangement of these papers appears to be a grouping under the leading authors. Such a grouping makes apparent the interests of these authors. Furthermore, it enables one to gain an idea of the general types of research which were pursued by a comparatively few principal investigators. By further listing the papers in chronological order, the periods of activity of the authors become evident.

The arrangement of the papers by authors likewise leads naturally to a segregation by national origin. It is observed that approximately 28 per cent of the number of papers was contributed by Russians, and approximately 24 per cent by Germans. The British Empire furnished nearly 17 per cent, the United States slightly over 10 per cent, and France about 8 per cent. The remaining 13 per cent came from Dutch, Japanese, Austrian, Italian, Swiss, Danish, Swedish, Norwegian, Latin-American, Hungarian, Lithuanian, Belgian, Czechoslovakian, Polish, and Rumanian sources.

To give even a brief survey of each paper would result only in producing an account both long and uninteresting. It seems preferable, therefore, to discuss but a few general topics and to leave the reader to consult the literature on the phases which most interest him. The attempt is made to acquaint the reader with the leading investigators and their lines of interest in the platinum metals; with the position of the United States as to production and consumption of the metals; with some of the important uses of the platinum metals; with the development in refining processes and in analytical procedures; and with the chemistry of coördination compounds of the platinum metals. This last-named subject is one about which much can be written. That phase of it which is given here is limited to the assembling of certain ideas and features, and it is written in

a manner intended to familiarize the reader with the complex nature of the compounds of the platinum metals.

II. Leading Investigators

By arranging the literature references in the manner which has been indicated, certain investigators stand out, chiefly because they were the central figures in university research, which happens to be the main source of published work. To become acquainted with the lives and activities of some of these men is to gain a clearer concept of the state of chemical knowledge of the platinum metals, and of the directions in which this knowledge has developed.

A. RUSSIAN CONTRIBUTORS

The foremost figure of the group of Russian contributors was Ljew Alexandrowitsch Tschugajeff (born at Moscow, October 4, 1873; died at Wologda, September 26, 1922). His name is usually anglicized to Chugaev. He was educated at Moscow, taught there, and later became professor of inorganic chemistry at the University of St. Petersburg. It should be of general interest to chemists that Chugaev's first research (1) on the platinum metals, published in 1905, resulted in the discovery of the inner complex salt of dimethylglyoxime with nickel and with palladium. Since Chugaev had been trained as an organic chemist, it is not surprising that his first research on the platinum metals was one in which he studied their reactions with organic reagents. This first research was concerned with the reactions of α-dioximes with nickel, cobalt, platinum, palladium, iron, and copper. His discovery in 1918 of the brilliant red compound

$$[Os(NH_2CSNH_2)_6]Cl_3 \cdot H_2O$$

by the reaction of thiourea (13, 15) with chloroösmic acid, has provided the platinum chemist with an extremely sensitive test for osmium.

The character of practically the entire Russian output of researches on the chemistry of the platinum metals reflects the influence of Chugaev. They have consisted in the preparation and study of complex compounds of the platinum metals (principally platinum) with organic sulfides and selenides; thio-, seleno-, and telluro-ethers; methyl nitrile and isonitrile; hydroxylamine; hydrazine; aminoacetal; ethylene; methyl-, ethyl-, and diethylamines; propylenediamine; pyridine; and also of a study of various ammino and mixed ammino complexes.

Following the collapse of Old Russia, the Soviet Government created in Leningrad an organization known as the Platinum Institute of the Academy of Sciences, under whose jurisdiction subsequent work on the platinum metals was conducted. Other phases, such as refining, analysis, and study of physical properties of the metals, were included in the work of the Institute. In line with the Soviet policy of creating a Russian chemical literature, a journal was founded by Chugaev in which to publish the papers emanating from the Platinum Institute. The first issue appeared in 1920, under the editorship of N. S. Kurnakov, E. Kh. Fritsman, and O. E. Zvyagintzev. This journal, as well as the Platinum Institute, went out of existence in 1935, after which date papers appeared for the

most part in a journal issued by the Institute of General Chemistry at Moscow, in a section devoted to the platinum metals (see introduction to bibliography).

Chugaev died at the age of forty-nine, and his mantle fell to Fritsman, who devoted his energies to the posthumous publication of Chugaev's accumulated researches. The principal lines of research in which Chugaev had been interested were carried on by his associates, chiefly I. I. Chernyaev, V. V. Lebedinskiĭ, and A. A. Grinberg.

A Committee on Analysis, consisting of S. F. Zhemchuzhniĭ, O. E. Zvyagintzev, B. G. Karpov, V. V. Lebedinskiĭ, N. I. Podkopaev, A. T. Grigoriev, and N. S. Kurnakov, was organized at the Institute to set up methods of analysis for native platinum, in the refining of which the Soviet Government had become vitally interested. This Committee made two reports (209, 210), one in 1926, and one in 1932, which consisted mainly of adaptations of traditional methods. Following this, Karpov published a few analytical papers, but nothing of any particular value resulted.

B. GERMAN CONTRIBUTORS

Interest in the chemistry of the platinum metals was more diversified in Germany than it was in Russia. A number of educational institutions formed centers of activity, chiefly because of certain professors. In addition, Germany possessed two of the five European platinum refineries, both of which are located in the medieval town of Hanau-am-Main.

Contemporaneous with Chugaev was Felix Alexander Gutbier (born at Leipzig, March 21, 1876; died at Jena, October 4, 1926). Gutbier was educated at the University of Erlangen, which had long been actively engaged in work on the platinum metals, particularly in the determination of their atomic weights. He taught at Erlangen from 1907 to 1912, and then at the Technische Hochschule in Stuttgart from 1912 to 1922. The last four years of his life were spent at the University of Jena. Gutbier published a great many papers, nearly all of them with students. His interests were in the colloidal platinum metals, chloro and bromo compounds of the platinum metals, the action of hydrogen and of oxygen on the metals, and an occasional research on the separation and determination of palladium.

The spirit and manner of Gutbier's researches were carried on by one of his students, Ferdinand Hermann Krauss, at the Technische Hochschule in Braunschweig. Krauss was born on August 6, 1889 at Stuttgart, received his degree at Erlangen in 1914, and, while still in the midst of a very productive scientific life, died at Köthen on June 17, 1938, after a brief illness. Krauss' interests in the platinum metals lay in the preparation and study of ruthenium tetroxide, osmium tetroxide, the halides of ruthenium and of iridium, the sulfates of rhodium, and the cyanide complexes of the platinum metals.

Another leading chemist was Lothar Wöhler (born in Bernburg, October 27, 1870). He was educated at Heidelberg and from 1911 on he directed the Chemical Institute at the Technische Hochschule at Darmstadt. Wöhler's early papers, dating from 1901, were concerned with catalytic activity and oxidation.

This early interest developed into studies of the various oxides of the platinum metals, the halides, and finally of the sulfides, selenides, tellurides, and arsenides. He also devoted attention to methods of refining and analysing the platinum group.

Quite a different line of interest in the platinum metals was followed by Wilhelm Manchot (born at Bremen, August 5, 1869) and his students at the Technische Hochschule in München. Manchot, a student of J. Thiele, published his first paper on the platinum metals in 1903 under joint authorship with Henri Moissan. It dealt with the preparation and properties of the compound of ruthenium with silicon. Twenty-one years later, Manchot published researches on the nitrosyl and carbonyl compounds of the platinum metals. These investigations were a part of a more general one dealing with the reactions of nitric oxide and of carbon monoxide. He was also interested in the lower states of valency of the elements. The papers which dealt with uni- and bi-valent ruthenium provoked polemic discussion, principally between one of his students, Heinrich Gall (born at München, November 9, 1899), and Heinrich Remy of Hamburg.

A distinguished contributor to the chemistry of the platinum metals for a period of twenty years has been Karl Otto Ruff (born at Schwäbisch Hall, Württemburg, December 30, 1871), a graduate of the University of Berlin and since 1916 professor at the Technische Hochschule at Breslau. With a wide variety of interests in chemistry, Ruff has enriched the literature on the platinum metals with excellent papers. His chief contributions have been his studies on the oxides and halides, particularly the fluorides, of the platinum metals. His first paper (807), dealing with the oxides and chlorides of osmium and the determination of osmium in these compounds, was published in 1910.

A leading contributor to the chemistry of ruthenium from 1920 to 1928 was Heinrich Remy (born at Weeze, Niederrh., September 20, 1890), who was educated at Freiburg and since 1922 has been professor of analytical chemistry at the University of Hamburg.

Hans Reihlen (born at Stuttgart, February 2, 1892), professor of chemistry at the University of Tübingen since 1928, contributed a number of papers dealing with the stereochemistry of platinous and palladous compounds.

Quite recently, 1936 to 1938, Karl Gleu and his associates at the Friedrich Schiller University in Jena have published ten papers on ruthenium ammines. One of these papers (337) reported a new determination of the atomic weight of ruthenium, obtained by determining the ruthenium content of chloropentammineruthenium chloride, $Ru(NH_3)_5Cl_3$.

C. AUSTRIAN CONTRIBUTORS

Ludwig Moser (born in 1879; died September 26, 1930) received his doctorate at Vienna in 1905. From 1921 until his accidental death he was professor of analytical chemistry at the Technische Hochschule in Vienna. His contact with the platinum metals came as a result of a systematic study of analytical procedures for the various elements. By utilising the reaction of bromide with bro-

mate, he developed a procedure for hydrolysing the chloro compounds of sodium and iridium and thus effecting their separation from platinum.

R. Strebinger and Hans Holzer, at the Technische Hochschule in Vienna, were primarily interested in microchemical methods, including the analysis of precious metal alloys. Holzer (393) subsequently published a procedure, not microchemical, for the analysis of precious metal alloys. This procedure is not unlike that which was simultaneously developed at the National Bureau of Standards for the analysis of dental gold alloys (760).

D. DUTCH CONTRIBUTORS

The outstanding Dutch contributor was Frans Maurits Jaeger (born at Haag, Netherlands, May 11, 1877). He received his doctor's degree at Leiden in 1903, and since 1908 has been professor of physical and inorganic chemistry at the University of Groningen. His interest was mainly in stereochemical problems and those of optically active salts, which included, of the platinum metals, those of rhodium.

E. SWISS CONTRIBUTORS

Of the Swiss contributors, two are outstanding. One was Alfred Werner (born at Mülhausen, Germany, December 12, 1866; died at Zürich, Switzerland, November 15, 1919). After receiving his early education in Germany, he went to Zürich and in 1890 obtained his doctor's degree. He married and remained in Switzerland and became professor of chemistry in the University of Zürich. He devoted his talents to the problem of clarifying the concepts of the structure of complex inorganic compounds, for which he was given the Nobel Prize in 1913.

The other distinguished contributor was Louis Claude Duparc (born at Carouge, near Geneva, February 13, 1866; died October 20, 1932). Duparc received his doctor's degree at the University of Geneva in 1887. He held for many years the professorship of mineralogy, petrography, and analytical chemistry at the University of Geneva, where he also directed the Laboratory of Analytical Chemistry. His life's work, which consisted in an exhaustive study of the world's platiniferous deposits, both mineralogically and chemically, was brought into book form in 1920 under the title *Le platine et les gîtes platinifères de l'Oural et du monde* (763) and bears the coauthorship of Marguerite N. Tikonowitsch. This monumental publication is unique. Duparc's well-equipped laboratory was the chief European center of activity in the chemical analysis of platiniferous materials during the first two decades of the present century. Here H. C. Holtz in 1911 presented his doctoral thesis (791) on the composition of the principal platinum minerals of the Ural, and M. Wunder and V. Thüringer (812) applied the reagent dimethylglyoxime, discovered by Chugaev in 1905, to the separation and determination of palladium.

F. FRENCH CONTRIBUTORS

The one dominant figure among the French contributors has been Stéphane Marcel Delépine (born at Saint-Martin le Gaillard, Seine-Inférieur, September

19, 1871). Delépine received his doctor's degree at the University of Paris in 1898, where he was a student of Marcelin Berthelot. From 1913 to 1930 he was a professor at the École Supérieur de Pharmacie, and since 1930 professor at the Collège de France, Paris. Between 1905, when he began active publication, and 1939, Delépine contributed approximately forty papers dealing with the platinum metals. With but few exceptions, these papers bear only his name. His early interest in the platinum metals appears to have come about through studies of the reaction between sulfuric acid and salts of platinum and of iridium. Continuation of this interest led to an exhaustive investigation of the sulfates of iridium. He likewise investigated the chloro salts of iridium and compounds of iridium in which pyridine was introduced. One line of research was devoted to the preparation and study of the optically active oxalate complexes of iridium and of rhodium.

Students of Delépine published independently, principally in the form of dissertations appearing in the Annales de Chimie. One of these students, Raymond Charonnat, between 1924 and 1931, contributed a series of papers dealing with the stereochemistry of ruthenium.

G. BRITISH CONTRIBUTORS

The character of the contributions originating in England is quite definitely that of theoretical interest in the structure of compounds. The leading contributors have been those whose primary interests were not necessarily in the field of the platinum metals, but who came into contact with these metals because they offered possibilities for the preparation of certain types of compounds. The English contributions are further characterized by being, for the most part, those of groups of associated workers. The leading figures have been the late Sir Gilbert T. Morgan, Frederick G. Mann, Harry Dugald Keith Drew, Ernest Gordon Cox, and William Wardlaw; the leading universities, Cambridge, London, and Birmingham.

The work of Drew was confined chiefly to the disposition of the valences in platinous and palladous compounds. His conclusion was that the structure was planar and not tetrahedral. Cox and a number of his associates attacked the problem of structure with the aid of x-rays.

Mann's interest was in the preparation of compounds formed by reaction with 1,2,3-triaminopropane, β,β'-diaminodiethylamine, trimethylarsine, sulfamide, etc.

With regard to Australian, South African, and Canadian contributions, the main interests have been in mining and assaying.

An extended series of papers was published by Sir Prafulla Chandra Rây (born at Rarula, Kulna, Bengal, India, August 7, 1861; doctorate from Edinburgh, 1887; professor of chemistry at Calcutta since 1889) and his associates on compounds of platinum with mercaptanic radicals. In these compounds Rây claims that the platinum is present in both the tervalent and the quinquevalent states.

H. AMERICAN CONTRIBUTORS

At only a few universities in the United States has there been any interest in the chemistry of the platinum metals. The one outstanding figure in university circles has been Jas. Lewis Howe of Washington and Lee University at Lexington, Virginia. Howe was born at Newburyport, Massachusetts, on August 4, 1859 and educated at Amherst College. He subsequently received his doctorate at Göttingen in 1882. From 1891 until his retirement from active service a few years ago, he was head of the Department of Chemistry of Washington and Lee University.

It is always of interest to learn the circumstances which start a person along a certain line of endeavor. Professor Howe has graciously informed the writer of the remark which led him to devote his energies to the chemistry of ruthenium. Fresh from the University of Göttingen, he was looking around for a subject to work on as opportunity permitted. At a meeting of the American Association for the Advancement of Science, he happened to tell Frank Wigglesworth Clarke of his aims. Dr. Clarke remarked to him that he did not see why chemists were devoting themselves so exclusively to an element with only four valences—the main interest of chemists at that time was organic chemistry—when so much more of real chemistry could be learned from elements with more valences, especially the platinum group with eight valences. Thinking over this remark and reading the literature of the platinum metals, Professor Howe came to the conclusion that ruthenium was the most interesting metal of the group, and that it was the one of which least was known.

Howe published his first paper on ruthenium and its nitrosochlorides in 1894. His second paper, in 1896, dealt with ruthenocyanides. His third publication was a bibliography (770) of the platinum metals which covered the period 1748 to 1896. This bibliography was brought up-to-date in a second edition (686) which covered the period 1748 to 1917. Howe's interest in the bibliography has been sustained and the references collected in the period 1918 to 1940 are now in manuscript form. This painstaking task, of untold value to those interested in the platinum metals, has been carefully and faithfully done. Some way to bring this manuscript into print must be found. Its failure to become available would be a great misfortune.

Through the years Howe has continued to contribute to the chemistry of the chloro and bromo salts of ruthenium.

One of Howe's students, S. C. Ogburn, Jr., published a number of papers dealing with methods of analysis for the platinum metals. In his doctoral thesis at the University of North Carolina in 1926, Ogburn described experiments in which he tested the reactions of about one hundred twenty different reagents, some inorganic and many organic, in an attempt to ascertain their possibilities as selective reagents for the platinum metals. Scrutiny of the organic compounds used yields no inkling of what particular atomic grouping confers the property of specificity.

William R. Crowell at the University of California at Los Angeles, and Don

M. Yost at the California Institute of Technology at Pasadena, published a few papers dealing with the study of states of valency of ruthenium and of osmium.

For a time the Bureau of Mines was interested in the platinum metals, and C. W. Davis published a number of papers dealing with their detection and estimation in ores.

Before the World War the National Bureau of Standards had published a few papers which dealt with physical properties of the platinum metals. In 1917 William Francis Hillebrand, chief of the Bureau's Chemistry Division, initiated a program of chemical investigation of the platinum metals, the nature of which was the development of methods for preparing the metals in a degree of purity adequate for the most exacting requirements, and the development of methods of analysis of platiniferous materials. Since 1917 the Bureau has published approximately fifty papers. About half this number deal with the measurement of physical properties, and many of these involve the purified metals prepared in the Bureau's laboratories. Only those papers directly concerned with chemical investigations are listed in the bibliography (739 to 762).

III. Platinum Metals in the National Economy

Economic statistics concerning the platinum metals are to be found in the yearly volumes of *Mineral Resources of the United States* (773) and in *Minerals Yearbook* (774), the latter superseding the former and both being publications of the Department of the Interior, United States Government. A separate publication, *Mineral Industry* (772), edited by G. A. Roush, likewise contains economic statistics. In these publications the information is classified in quite a number of different ways.

A. PRODUCTION

In the matter of sources of the platinum metals, only a few figures will be given here to illustrate the position of the United States. The total production of crude platinum in the world up to January, 1917, was estimated to be somewhere between 8 and 11 million troy ounces. Of this amount Russia produced between 7 and 10 million ounces. Colombia was next with approximately 735,000 ounces, and Borneo third with about 200,000 ounces. New South Wales together with Tasmania had produced about 10,000 ounces, and Canada and the United States had contributed a similar quantity. Before the World War, in 1912, Russia had reached an annual production level of 300,000 ounces, which figure fell to 53,000 in 1916 and reached a low of 5500 ounces in 1921. The production in Russia has varied considerably since then and in recent years only estimated figures are available, which appear to be about 170,000 ounces or over.

Colombia, in 1912, produced 12,000 ounces. The production figure has steadily increased, with fluctuations, and in 1939 was 39,000 ounces. From 1918 on, the production has ranged between 30,000 and 55,000 ounces, the banner year being 1934.

Canada, which in 1912 was credited with the production of only 30 ounces, has risen to become one of the principal platinum-producing countries of the world,

owing to the electrolytic refining of nickel and copper produced from the ores of the Sudbury District of Ontario. In 1938 Canada produced over 161,000 ounces.

The discovery of extensive lode platinum deposits in South Africa in the early 1920's, the working up of which has placed this section as a chief source of platinum, with an amount of 47,000 ounces in 1939, was a sensation in platinum mining.

Ethiopia produces a significant amount of platinum, which varies from 3000 to 8000 ounces a year.

Although the United States is by far the largest consumer of platinum metals in the world, before 1935 it contributed only a negligible quantity to the world output. For example, during the ten years 1925 to 1934 production averaged only about 8300 ounces annually—1000 ounces from placer platinum, 600 from palladium-bearing copper ore, and 6700 as by-products of gold and other metals. Since 1935, chiefly because of large-scale mining in Alaska, the production of platinum metals in the United States has advanced progressively from 11,552 ounces in 1935 to 48,269 in 1938. The latter figure is the sum of 40,932 ounces of placer platinum, 7249 ounces recovered from gold and copper refining, and 90 ounces obtained from platinum-bearing ore. Thus, the United States attained the rank of fourth largest producer of platinum metals in 1938. Although production dropped to 43,760 ounces in 1939, the United States retained its rank.

In addition to being now the fourth largest source of supply of platinum metals, the United States is an important refining center and occupies a prominent position in the international platinum trade. In 1939, for example, 41,441 ounces of new platinum metals and 63,443 ounces of secondary platinum metals were recovered by domestic refiners, 306,627 ounces of unmanufactured platinum metals was imported for consumption, and 46,329 ounces of platinum and allied metals (ingots, sheets, wire, alloys, and scrap) and a considerable quantity of placer platinum were exported.

The world production of platinum metals in 1938 was about 540,000 ounces, of which about 57 per cent was recovered as by-products in the refining of nickel, copper, and gold ores. In 1929 the world production was about 231,000 ounces, of which about 17 per cent was so obtained.

B. PRICES

Owing to market conditions, the prices of the platinum metals are liable to change suddenly.

The average price of refined platinum in New York in 1915 was $49.63 a troy ounce. In 1917 it was $102.82. After the War Department had commandeered all crude and refined platinum on March 2, 1918, a maximum price of $105 an ounce for all imports was set by the War Industries Board. The highest price paid for platinum was $154 in 1920, and the lowest, about $22, in 1933. The price averaged $36 an ounce in 1939.

Refined palladium was quoted at $70 to $85 an ounce at the beginning of 1917, but prices advanced to $130 to $135 by the end of the year. The price averaged $24 in 1939.

In the last months of 1917 iridium was sold at \$180 to \$185 an ounce, thereafter increasing to as much as \$400 to \$450 in October, 1920. It maintained a price of \$260 to \$280 for a considerable period. Its average price in 1939 was \$112. In 1940 iridium rose from \$125 to \$175 an ounce, returned to \$125, rose again to \$140, and in December of that year brought \$275. The advance in price was attributed to heavier demand by the aircraft industry, greatly reduced imports, and speculative influences.

Since 1933 ruthenium and osmium have been valued at an average figure of about \$40 to \$60 an ounce, respectively. Rhodium remained fairly constant during 1940 at about \$125 an ounce.

C. CONSUMPTION AND USES OF THE PLATINUM METALS IN THE UNITED STATES

The most widely used metal of the group is platinum, which amounted to 63.3 per cent (100,266 ounces) of the total platinum metals sold by domestic refiners in 1939. The largest single consumer of platinum is the jewelry industry, where, alloyed with iridium, it is used as a setting for diamonds and other precious stones in rings and various other forms of jewelry. About 47 per cent (47,385 ounces) of the total sales of platinum by domestic refiners went to the jewelry trade in 1939.

Second in magnitude as a consumer of platinum in 1939 was the chemical industry, which took 20 per cent (20,306 ounces) of the total domestic sales. Platinum is used as a catalyst to produce sulfuric acid, and also as a catalyst to oxidize ammonia to produce nitric oxide and nitric acid. It is used to line processing and reaction vessels; in the hydrogenation of organic compounds; in rayon spinnerets; in spinnerets for the production of glass fiber; in nozzles for casting glass lamp bases; and in gas-analysis cells. It is also used in the form of tubing, valves, siphons, and safety disks for handling corrosive liquids and gases, and as anodes for the production of "per" salts. To chemists its use is perhaps best known in the form of crucibles, dishes, and other laboratory equipment.

The dental industry ranked third as a consumer of platinum in 1939, taking 14 per cent (13,755 ounces) of the total domestic sales. In 1940 the dental industry dropped to fourth place as a consumer, being displaced by the electrical industry. Platinum, either pure or alloyed, is used in tooth pins, bridges, and bracings for artificial teeth, as matrices on porcelain inlays, and in orthodontic appliances.

The electrical industry, the fourth largest consumer of platinum in 1939, took 12 per cent (11,952 ounces), and in 1940 became the third largest consumer. In this industry platinum is used for thermocouples, temperature-measuring and -recording instruments, precision resistance thermometers, high-temperature furnace windings, spark plug electrodes, magneto contacts, electrical contacts, relays, thermostats, automatic voltage regulators and direction indicators, and switches for potentiometric recorders.

Platinum leaf was made available during 1939 for outdoor signs, for interior decoration, and for book stamping. Palladium leaf was introduced for somewhat similar purposes in 1933.

Next to platinum, palladium is the most extensively used metal of the platinum group. It is about half as common as platinum, but less costly. Pal-

ladium comprised 32.5 per cent (51,406 ounces) of the total platinum metals sold by domestic refiners in 1939. Palladium, pure or alloyed, is adapted to many of the uses of platinum, and during the past two decades it has been employed in increasing quantities by the dental, electrical, and jewelry industries. The conservation of gold by many countries has stimulated the demand for the platinum metals, particularly palladium, and the use of palladium as a substitute for gold alloys for dental restoration, pen points, and articles of jewelry has made substantial progress. The largest consumers of palladium in 1939 were the dental and electrical industries, which purchased 22,989 and 21,510 ounces, respectively, from domestic refiners. The jewelry industry is the third largest consumer of palladium, and small quantities of this metal are used in the manufacture of chemical ware.

Iridium ranks third in consumption among the metals of the platinum group. Of the total sales of platinum metals in 1939, 2.7 per cent (4322 ounces) was iridium. This metal is used chiefly as a hardening addition to platinum, to render it suitable for laboratory vessels, surgical tools, and jewelry. At present, ruthenium is also being used as a hardening agent for platinum in the manufacture of alloys for jewelry, thus releasing iridium for other purposes.

The consumption of the other platinum metals—rhodium, osmium, and ruthenium—is small and comprised only 1.5 per cent of the total for the group in 1939. Rhodium is alloyed with platinum for high-melting-point thermocouple wire, furnace windings, and for laboratory ware for certain special purposes. Rhodium plating is employed as a finish for glassware and silverware, and in surfacing reflectors for searchlights and projectors. During 1939 platinum–rhodium spinnerets replaced the older platinum–gold spinnerets, because of their superior resistance to the various corrosive agents used in the production of rayon. Osmium, in association with other metals, provides pen points that will resist wear and corrosion by ink. These alloys also replace jewels as bearings in fine instruments. Osmium tetroxide is used as a biological stain for fats, and for fingerprint work.

IV. Properties Which Make the Platinum Metals Useful

The platinum metals owe their usefulness in commerce to a combination of intrinsic physical properties and relative chemical inertness.

The metals composing the lighter triad, namely, ruthenium, rhodium, and palladium, have densities of 12.2, 12.4, and 12.0 g./cm.³, respectively. These values are slightly higher than that of lead, which is 11.34 g./cm.³ The metals of the other triad, osmium, iridium, and platinum, have densities approximately twice that of lead. The density of platinum is 21.45 g./cm.³, and that of iridium, 22.41 to 22.65 g./cm.³ There appears to be some question about the density of osmium, which lies within the limit 22.41 to 22.61 g./cm.³ It is not definitely settled whether osmium or iridium possesses the distinction of having the greatest density of any of the elements.

In the crystalline state ruthenium and osmium belong to the hexagonal system, while the other four metals belong to the cubic system.

The crystalline fracture of fused ruthenium has a color between those of iron

and platinum.   Palladium is silvery white, its color being between those of silver and platinum.   Compact osmium is bluish gray.   Compact iridium has a brilliant grayish white surface, between those of silver and tin.   Fused rhodium is white, and resembles aluminum in color.   Its color is less brilliant than that of silver.   The nobility of rhodium, combined with its high reflectivity, makes it particularly suitable for front-surface mirrors.   The advent of rhodium plating has also made it possible to produce serviceable metal reflectors for searchlights and motion picture projectors, because a rhodium-plated surface is resistant to the combined effects of corrosion and heat.

Only in the cases of rhodium, palladium, iridium, and platinum have the freezing points of the platinum metals been accurately determined.   They are, respectively, 1966°, 1554°, 2454°, and 1773°C.   The melting point of ruthenium is believed to be above 2400°C., and perhaps above 2450°C., and that of osmium is believed to be about 2700°C.   The estimated boiling points of the platinum metals are: ruthenium, 4900°C.; rhodium, 4500°C.; palladium, 3000–3980°C.; osmium, 5500°C.; iridium, 5300°C.; platinum, 4530°C.

The values which have been reported for the hardness of the metals depend to a great extent on the chemical purity, physical condition, and previous treatment of the metals.   It is difficult, therefore, to say precisely what these figures should be.   It appears that ruthenium has a hardness on the Brinell scale of about 220.   That of iridium is probably slightly less than this value, and that of osmium slightly greater.   The hardness of rhodium is somewhat in excess of 100, that of palladium is about 50, and that of platinum about 35.   These approximate figures, at least, give an idea of the relative hardness of these six metals.

Pure platinum, which is soft, is hardened by alloying with it other metals of the platinum group.   Arranged in order of their decreasing ability to harden platinum these metals are: osmium, ruthenium, iridium, rhodium, and palladium.   Of these, iridium has long been the principal one used in this country.   Recently, however, ruthenium has been replacing iridium in alloys intended for the jewelry trade.   The ability to set precious stones in hard iridioplatinum alloys accounted for the introduction of these two metals into the jewelry industry.   Iridioplatinum hypodermic needles, containing 30 per cent of iridium, have now been largely displaced by stainless-steel needles.

According to Atkinson (779) spark plug electrodes made of 20 per cent iridioplatinum give excellent results in airplane engines.   The same author reports that the increase in the production of viscose rayon has led to an increased use of precious metals for spinnerets.   Through the use of 10 per cent rhodioplatinum it has been possible to make a spinneret which contains 3000 holes, each with a diameter of 0.003 in.   A spinneret of this kind is 1½ in. in diameter.   Thus, it has become possible to utilize ordinary textile machinery in fabricating rayon material.   The same alloy is also used for "spinnerets" for producing fine glass filaments which can be woven into flexible cloth for use in electrical and thermal insulation.   A recent application of the same alloy, in the lamp industry, because of its resistance to corrosion and abrasion at high temperature, has been its use in making glass-feeding nozzles for casting lamp bases.

Platinum and rhodioplatinum are in undisputed possession of the field in the manufacture of nitric acid by the catalytic oxidation of ammonia. Originally, pure platinum was used as a catalyst, but it is now being replaced by 10 per cent rhodioplatinum, which has a higher conversion efficiency and lower metal loss than has pure platinum. The production of nitric acid by the catalytic oxidation of ammonia has well-nigh supplanted natural nitrates as a source of nitric acid. Platinum catalysts, in the form of platinized asbestos, platinized magnesium sulfate, and platinized silica gel, are used to oxidize sulfur dioxide to sulfur trioxide in the manufacture of sulfuric acid.

There are three physical properties,—electrical resistance, electromotive force, and freezing point,—through the utilization of which the platinum metals enter into the measurement of temperature. The International Temperature Scale is based upon a number of fixed and reproducible equilibrium temperatures to which numerical values are assigned, and upon specified formulas for the relation between temperature and the indications of instruments calibrated at these fixed temperatures. The basic fixed points are: the oxygen point, the ice point, the steam point, the sulfur point, the silver point, and the gold point. From temperatures of $-190°C$. to $660°C$. the electrical resistance of platinum is made use of. From $660°C$. to the gold point the temperature is deduced from the electromotive force generated in a thermocouple, one leg of which is pure platinum and the other an alloy of 10 per cent of rhodium and 90 per cent of platinum. Above the gold point the temperature is determined by means of the ratio of the intensity of monochromatic visible radiation emitted by a black body to that of the same wave length emitted by a black body at the temperature of freezing gold.

The freezing point of palladium is used as a secondary point in the scale of temperature. The freezing points of platinum and iridium have been proposed for the same purpose.

A black body maintained at the temperature of freezing platinum is under consideration as an international standard of light.

For further information on the physical properties of the platinum metals and their alloys, as well as the uses of these metals, the reader is referred to the recent book by Vines and Wise (810).

V. REFINING THE PLATINUM METALS

A. RAW MATERIALS

During the past twenty years there have been some very important changes in the platinum industry, not the least of which is the growing importance of the production of platinum from primary deposits. Whereas in 1915 the output of platinum from alluvial deposits was more than 95 per cent of the world production, by 1934 it had fallen to about 50 per cent or lower. It seems likely that the alluvial deposits will diminish in importance as the richer ones are worked out, and that future requirements will be supplied from primary deposits.

The first authentic reference to the occurrence of platinum is that of Don Antonio de Ulloa y Garcia de la Torre (777), who accompanied the French expe-

dition in 1735 to measure the arc of the meridian at the equator. In 1748 at Madrid he published an account of his experiences, and mentioned that in the mines of El Choco, Colombia, South America, there was an infusible metallic stone which made even gold ores useless if associated with them in large quantities. Platinum was discovered in the Ural Mountains of Russia in 1819. These two localities remained the chief sources of platinum until recent years. Ural platinum, which is typical of alluvial native platinum, has the following ranges of composition: platinum, 73 to 86 per cent; iron, 8 to 17 per cent; palladium, 0.3 to 1.8 per cent; rhodium, ruthenium, osmium, iridium, 2.5 to 7.7 per cent. The recently discovered native platinum of the Goodnews Bay district of Alaska, which now rivals the Colombian output, occurs in a region geologically similar (799, 800) to that of the Urals and of Colombia.

Osmium and iridium occur native in the alloy osmiridium, which has been found in economically important quantities in the Urals, in Tasmania, and in the auriferous conglomerates of the Rand. The composition of this mineral is variable: osmium, from 23 to 40 per cent; iridium, from 21 to 35 per cent; ruthenium and rhodium together, from 9 to 15 per cent; and platinum, from 5 to 15 per cent.

Native platinum is found in regions of ultrabasic igneous rocks rich in olivine, and is recovered from stream beds and freed from gangue by mechanical treatment. For a detailed account of the geological aspects of deposits of native platinum the reader is referred to the treatise by Duparc and Tikonowitsch (763).

The sources of Canadian platinum are the well-known copper–nickel ores of the Sudbury district of Ontario. Palladium, in about the same amount as platinum, and subordinate amounts of the other platinum metals are also in these ores, besides silver and gold. These ores furnish the main supply of rhodium, which in recent years has been used to plate large reflectors and even cheap jewelry. The main sulfide mineral is pyrrhotite or magnetic pyrites, Fe_2S_4. With this is associated the copper mineral chalcopyrite or copper pyrites, $CuFeS_2$, and the nickel mineral pentlandite, NiS. The extraction of the platinum metals from the Sudbury sulfide ore constitutes an entirely new industry of rapid growth.

Platinum accompanies the nickel and copper of the Sudbury pyrrhotite in the form of sperrylite, $PtAs_2$. Palladium is present, probably as the selenide. The actual amount of platinum is, however, very small; the total platinum metal content of the ore is little more than one part in two million, that is, the platinum content is about the same as the concentration of radium in pitchblende. Owing to the fact that large tonnages of ore, over 1,800,000 tons in 1934, are treated for the recovery of the main products, copper and nickel, very substantial amounts of the platinum metals are obtained as by-products. In the treatment of the Sudbury copper–nickel deposits, the platinum metals follow the nickel through the various refining operations. The platinum metals become concentrated in the copper–nickel matte of the smelting process and, finally, when the nickel is electrolytically refined, the platinum metals remain in the anode slimes. The treatment of these ores has been discussed by Atkinson and Raper (780).

South African platinum is obtained from very extensive primary deposits in sulfide-bearing norite in the Potgietersrust and Rustenburg districts of the Transvaal. Particulars of these deposits, and methods of recovering platinum from them, are given in *Platinum and Allied Metals* (775).

In the sulfide-bearing rocks of the South African deposits, platinum occurs in both the metallic and the combined states. All the metals of the platinum group, as well as iron, nickel, cobalt, copper, silver, and gold, occur in these primary deposits. The amount of base metals is not sufficient to pay the working costs, which consequently fall mainly on the platinum metals, gold, and silver. The preliminary stage in the treatment of the ores, which contain, on the average, four to ten parts of platinum metals in one million, is that of mechanical concentration. Gravity separation yields a concentrate of metallic platinum containing up to two-thirds of the metal present, and flotation processes give a platiniferous mixture of copper, nickel, and iron sulfides which is smelted to a matte. The matte is resmelted, with the addition of sodium carbonate, under reducing conditions which lead to the liberation of a predetermined quantity of iron and nickel, into which the platinum metals pass quantitatively. The matte is allowed to weather in the air, when, owing to the presence of sodium carbonate, a friable mass is rapidly obtained from which the iron–nickel–platinum alloy can be isolated by gravity concentration and magnetic separation. If this alloy is rich in iron, it is smelted with sodium sulfate and silica; most of the iron is thereby slagged off, leaving a nickel matte rich in the platinum metals. If the alloy is rich in nickel, however, it is concentrated by smelting with sufficient sulfur-bearing material to convert 80 to 90 per cent of the nickel into the sulfide. By either method, a platiniferous alloy is ultimately obtained which can be treated electrolytically to give an anode slime for final refining by the usual wet processes.

Very few compounds of the platinum metals occur as minerals. Those which have been found are: sperrylite, $PtAs_2$; cooperite, PtS; braggite, $(Pt,Pd,Ni)S$; laurite, RuS_2 or $(Ru,Os)S_2$; stibiopalladinite, Pd_3Sb; and potarite, $PdHg$. As previously mentioned, platinum occurs in the Sudbury ores as sperrylite and the palladium probably as a selenide. In the South African ores palladium occurs, along with sperrylite, as stibiopalladinite. It is interesting to examine the variation in the relative proportions of the platinum metals in the various modes of natural occurrence. It is seen that in the native platinums the proportion of palladium to platinum is small, whereas in the platinum metals extracted from sulfide minerals the palladium is equivalent to or in excess of the platinum. On the basis of Goldschmidt's (790) scheme, the elements may be classified as siderophile, chalcophile, or lithophile, according to their equilibrium distribution between molten iron, molten sulfides, and fused silicates. The occurrence of a greater proportion of palladium in the Sudbury and South African ores than in native platinum may perhaps be correlated with the more pronounced chalcophile properties of palladium as compared with platinum.

The success of the metallurgical processes of concentrating the platinum metals in low-grade sulfide ores has depended upon the iron- and sulfide-loving character of the precious metals.

B. COMPOUNDS AND REACTIONS

The types of compounds most frequently encountered in the refining of the platinum metals are the chloro acids and their ammonium salts. The chloro acids of the platinum metals are formed when platiniferous materials are dissolved in hydrochloric acid, usually with the aid of an oxidizing agent. For example, platinum dissolves in aqua regia to form not platinic chloride, $PtCl_4$, but chloroplatinic acid, H_2PtCl_6. The anhydrous chlorides, such as $PtCl_4$, $RhCl_3$, etc., formed by the action of hot chlorine on the metals, are relatively insoluble compounds. They differ markedly from the readily soluble chloro complexes which are formed in the wet way. Chloro acids are formed by all six of the platinum metals. Depending upon the valency of the central metallic atom, different chloro acids may exist. Platinum forms $H_2[PtCl_6]$ and $H_2[PtCl_4]$; palladium, $H_2[PdCl_6]$ and $H_2[PdCl_4]$; iridium, $H_2[IrCl_6]$ and $H_3[IrCl_6]$; rhodium, only $H_3[RhCl_6]$; osmium, $H_2[OsCl_6]$ and $H_3[OsCl_6]$; ruthenium, $H_2[RuCl_6]$ and $H_3[RuCl_6]$. In the case of ruthenium particularly, as is seen later, the presence of nitric acid produces a more stable complex, in which the nitroso group is attached to the central metallic atom, for example, $K_2[RuCl_5NO]$. Osmium likewise shows this tendency.

Use is made in refining processes of the relative insolubilities of the ammonium salts of the chloro acids in which the central atom is quadrivalent. The alkali elements, potassium, rubidium, and cesium, likewise form insoluble salts, similar to those formed by the ammonium radical.

Other useful compounds are those formed when the chloro acids of the platinum metals react with sodium nitrite. The chloro acids are converted to complex nitrite compounds which, in the case of platinum, palladium, rhodium, and iridium, are $Na_2[Pt(NO_2)_6]$, $Na_2[Pd(NO_2)_4]$, $Na_3[Rh(NO_2)_6]$, and $Na_3[Ir(NO_2)_6]$. These compounds are sufficiently stable in slightly alkaline solution to permit the separation from them of many of the base metals in the form of their hydrated oxides. The ammonium salt, $(NH_4)_3[Rh(NO_2)_6]$, is sparingly soluble in neutral solution, and it is utilized in the refining of rhodium. The corresponding compound, $(NH_4)_3[Ir(NO_2)_6]$, is used in the purification of iridium.

The chloro acids of the platinum metals, except those of platinum, hydrolyze when their solutions are neutralized to an acidity corresponding to about pH 7, with the formation of hydrated oxides. Advantage is taken of this behavior to separate palladium, rhodium, and iridium from platinum.

The use of ammonium hydroxide in refining operations has been limited to the purification of rhodium, palladium, and osmium. The process of purifying rhodium by means of chloropentamminerhodium chloride, $[Rh(NH_3)_5Cl]Cl_2$, was used at one time, but it has been displaced by other methods which do not involve the formation of ammines.

In the case of palladium the use of ammonium hydroxide does have advantages. When the chloro acid of palladium is made ammoniacal and warmed, it is converted to tetramminepalladous chloride, $[Pd(NH_3)_4]Cl_2$. This compound is soluble in ammonium hydroxide. Upon adding hydrochloric acid in excess to the solution, dichlorodiamminepalladium, $[Pd(NH_3)_2Cl_2]$, is pre-

cipitated. In commercial refining operations osmium is recovered from an alcoholic alkaline solution in which its tetroxide is absorbed by converting it to osmyltetrammine chloride, $[OsO_2(NH_3)_4]Cl_2$. With these exceptions the use of ammonium hydroxide is not recommended, because of the formation of stable ammines, which can not be easily transformed again into chloro acids.

Osmium and ruthenium are distinctive metals in that they readily form volatile tetroxides, in which the metal is united with four atoms of oxygen. Osmium tetroxide melts at about 40°C., boils at 129°C., and can be distilled from aqueous solution. If pure, or in the presence of oxygen, it is stable at temperatures as high as 1500°C. (384). Ruthenium tetroxide melts at 25.5°C., but its boiling point has not been determined. At about 108°C. it decomposes with explosive violence and produces a soot, which is probably the dioxide. Like osmium tetroxide, ruthenium tetroxide can be distilled from aqueous solution. The volatilities of these two compounds are utilized in isolating them from other elements.

A word of warning should be mentioned in connection with osmium tetroxide. This substance has a deleterious effect on the tissues of the animal body. Casual exposure to it is first noticed in the eyes, which become irritated and bloodshot. One who has been exposed to the vapors of osmium tetroxide experiences an unusual optical effect. A street light, for example, appears to be surrounded by a halo in which the spectral colors are arranged in concentric bands in the order from violet near the center to red at the periphery. Superimposed upon this halo are shafts of white light which radiate from the center of the source of illumination. This latter effect is probably not caused by osmium, since those who have never been exposed to the vapor report its existence. It may be that the osmium accentuates the effect. Those who may have occasion to work with osmium should consult the publication by Brunot (753) on the toxic effects produced by osmium tetroxide.

C. METHODS OF COMMERCIAL REFINING

The chemical engineering problems in connection with the refining of platinum are of a specialized nature, with the result that experience in other fields is not always directly applicable. Moreover, the tradition of secrecy in the platinum industry up to the present has prevented refineries from pooling their experience except in a very general way. This state of affairs is in marked contrast with what is known about the plant and processes for the refining of silver and gold. Because of this tradition of secrecy concerning, particularly, the wet processes used for refining crude platinum and platinum concentrates, very few details find their way into the literature. The processes used for commercial refining, once the platinum metals have been concentrated to a point where wet processes apply, probably differ very little. The scale of operation is small; even the refining of platinum is frequently described as large-scale laboratory work, and the refining of the other metals of the group is on a still smaller scale. The separations and purifications are accomplished by a limited number of reactions. The main differences in the processes used to extract the platinum metals exist be-

cause of the particular sources of the concentrates and the relative proportions of the metals which they contain.

1. Refining of native platinum

The principal source of the platinum metals, until a few years ago, has been native platinum. This occurs as a mixture of metallic alloys in the stream beds of certain areas scattered over the world. In this form the metals are already partially concentrated by nature, and the problem of refining is one of working up this naturally occurring metallic product.

The first step in the process of refining native platinum consists in treating it with aqua regia. The treatment is continued until as much of the material dissolves as is possible. The insoluble fraction which is usually obtained consists of osmiridium, iridium, and certain non-platiniferous minerals, and is worked up separately. The soluble fraction contains the bulk of the platinum in the original material, together with palladium, gold, silver, a portion of the iridium and rhodium, and traces of osmium and ruthenium. In addition, the solution also contains iron, copper, and other base metals which have been dissolved.

(a) Precipitation of platinum by ammonium chloride

The chief component of the solution obtained by treating native platinum with aqua regia is platinum, and this is the first metal which is recovered. The usual process is to precipitate the bulk of the platinum as ammonium chloroplatinate, $(NH_4)_2[PtCl_6]$, by the addition of ammonium chloride.

To prepare the solution from this precipitation, the nitric acid and most of the excess of hydrochloric acid are removed by evaporation. A small amount of water is added to the hot sirupy residue to cause the decomposition of nitrous compounds of platinum, after which hydrochloric acid is added and the evaporation repeated. It is well to continue the evaporation each time until the temperature of the solution reaches 140° to 150°C., unless the residue becomes pasty, in which case local overheating is likely to occur. The evaporation at high temperature probably causes the reduction of part of the iridium to the tervalent state, in which form less of this element will be precipitated with the platinum salt.

After the solution has been evaporated, it is diluted to some convenient concentration,—for instance, 50 to 100 g. of platinum in 1 liter,—and set aside to permit silver chloride and other insoluble matter to settle. The solution is decanted or filtered from the insoluble residue, heated nearly to boiling, and treated with ammonium chloride. Ammonium chloroplatinate separates at once. A small excess of ammonium chloride is desirable to reduce the solubility of the ammonium chloroplatinate, but a large excess should be avoided because it increases the degree of contamination of the salt. (For more detailed discussion of the contamination of ammonium chloroplatinate by rhodium and iridium, see Section VI of this paper.) The solution is cooled quickly and filtered at once to avoid contaminating the precipitate with the very impure salt which separates on standing. The precipitate is well drained, and washed once or

twice with a 20 per cent solution of ammonium chloride, after which it is dried and ignited to metallic sponge. Further purification is needed to prepare pure metal. This phase is best discussed somewhat later in connection with the preparation of pure platinum.

(b) Treatment of filtrate from the precipitation of platinum by ammonium chloride

After the precipitation of platinum by ammonium chloride, the next step depends on the nature and proportion of the other metals in the filtrate. If there is a large amount of gold, it may be desirable to separate that metal by the addition of ferrous sulfate solution. The separation is rapid and complete, and the gold thus obtained is fairly pure. If much palladium is present, it may be desirable to add more ammonium chloride and a volume of nitric acid amounting to 20 or 30 per cent of the solution. Digestion on the steam bath causes the precipitation of ammonium chloropalladate, $(NH_4)_2[PdCl_6]$, accompanied by much of the iridium and platinum in the solution. However, the presence of nitric acid interferes greatly with the removal of the remaining precious metals. Usually, the most convenient procedure is to precipitate all of the metals remaining in the solution, after the first precipitation of platinum, by means of zinc or iron. As it is very difficult to precipitate iridium completely in this way, the process must be continued for a long time, possibly for some days. Even then it is quite likely that some of the iridium will escape precipitation.

The metals precipitated by zinc or iron are washed by decantation, and, after a sufficiently large amount of such material is accumulated, it is attacked with diluted aqua regia. Gold and palladium are very rapidly attacked and platinum reasonably so. Comparatively little iridium, rhodium, and ruthenium will dissolve. If platinum predominates in the solution, it is best precipitated first, by means of ammonium chloride, as described. If not already separated, gold is then removed by precipitation with ferrous sulfate, after which palladium is precipitated as described. The various precipitates of platinum, gold, and palladium will contain more or less iridium, rhodium, and ruthenium. The remainder of these metals, together with unprecipitated platinum and palladium, are recovered by precipitation with zinc as before, after evaporating the solution to eliminate most of the nitric acid.

(c) Treatment of the residue obtained after extracting the zinc-precipitated metals with diluted aqua regia

The residue of rhodium, iridium, and ruthenium may be worked up with the osmiridium material which remained undissolved in the original aqua regia treatment of the native platinum. However, if sufficient material is at hand to work the two lots separately, it is better to do so, because the former contains little or no osmium and a very minor amount of ruthenium and may therefore be handled somewhat more simply.

If rhodium is predominant, the dried residue is intimately mixed with about 2.5 times its weight of crushed sodium chloride and brought to a dull red heat in

a gentle current of chlorine. This treatment converts a large part of the rhodium to the soluble sodium rhodium chloride, $Na_3[RhCl_6]$. Some of the iridium will also be converted to a chloro salt, but this metal is less readily attacked than rhodium.

If iridium is predominant, the residue is better attacked by fusion, at 600–700°C., with three parts of sodium hydroxide and one part of sodium peroxide, in a silver, nickel, or iron dish. A portion of the iridium is dissolved, probably in the form of a basic iridate. By far the greater part of the iridium from such a fusion remains insoluble in water, but does dissolve in hot concentrated hydrochloric acid, to form chloro acids of iridium. The ruthenium will be found largely in the aqueous solution obtained by leaching the fused alkaline mass. If only small amounts of ruthenium are involved, it will be less tedious not to attempt to separate ruthenium at this point, but merely to concentrate it by precipitation together with iridium and any osmium by exactly neutralizing the alkaline solution with hydrochloric acid or sulfuric acid, adding a little alcohol, and boiling. The small amount of metals remaining in the solution after this treatment may be recovered by reduction with zinc and hydrochloric acid. The treatment of this mixture of iridium, ruthenium, and osmium is discussed in the following section dealing with the osmiridium fraction. Rhodium is not rapidly attacked by alkaline fusions. For this reason, it is often advantageous to alternate the treatments, sodium chloride–chlorine and sodium hydroxide–peroxide, until all the material has been rendered soluble.

When the material, which consists largely of rhodium and iridium, has been brought into solution as chlorides, the two metals may be separated by either of two procedures, depending on their relative proportions. Unless there is more rhodium than iridium, a convenient way of effecting the first separation is to precipitate iridium as ammonium chloroiridate, $(NH_4)_2[IrCl_6]$. Before adding ammonium chloride, the solution should be treated with a current of chlorine to oxidize any tervalent iridium to the quadrivalent state. The solution should be concentrated so as to contain not less than 50 g. of the two metals in 1 liter. Enough ammonium chloride is added to react with the iridium. A large excess should be avoided, because of its interference with the subsequent concentration of rhodium. The ammonium chloroiridate is separated by filtration, drained, and washed moderately well with a solution of ammonium chloride. It is likely to contain considerable rhodium as impurity. Most of the iridium remaining in the solution with the rhodium is recovered by evaporating the solution to dryness. This serves also to eliminate any excess of acid, which would be troublesome in the subsequent concentration of rhodium. The residue is taken up in sufficient water to dissolve any readily soluble salts, such as ammonium chloride, sodium chloride, or the complex chloride of rhodium, and filtered from the small precipitate of impure ammonium chloroiridate. The filtrate is diluted so as to contain not more than 40 to 50 g. of rhodium in 1 liter, heated nearly to boiling, and treated with sodium nitrite. This reagent first neutralizes the acid present and reacts with the ammonium chloride to form ammonium nitrite, which decomposes in the hot solution. Rhodium and the other platinum metals, as well

as certain base metals, are converted to soluble complex nitrites, while other base metals, notably iron, copper, and tin, are precipitated as hydroxides. Heating is continued and more sodium nitrite is added until the color of the solution becomes yellow or light brown. The precipitate is removed by filtering and treated for the small amounts of platinum metals which it may contain. Ammonium chloride is added to the well-cooled filtrate to precipitate ammonium rhodium nitrite, $(NH_4)_3[Rh(NO_2)_6]$. The details of this treatment are described in the section dealing with the preparation of pure rhodium. The granular, white or yellowish salt is separated by filtration, washed with water and dried, or dissolved in hydrochloric acid for further purification. It is not suitable for direct ignition to metallic sponge. Residual metals are recovered from the filtrate.

(d) Treatment of the fraction of native platinum which is insoluble in aqua regia

The residue which remains undissolved in the original aqua regia treatment of native platinum is converted into soluble form by fusion with sodium hydroxide and peroxide. As the grains of osmiridium are rather slowly attacked by the alkaline fusion, they are sometimes converted to a finely divided zinc alloy by melting with five to ten parts of zinc at 600–800°C. for 2 to 3 hr. The molten mass is covered with fused zinc chloride to prevent rapid oxidation of the zinc and is occasionally stirred with a graphite rod. Treatment of the cooled, solidified melt with hydrochloric acid dissolves the excess of zinc and leaves the osmium and iridium in a finely divided residue. The powder is washed and dried, but not ignited, and is then ready for the alkaline fusion. The aqueous extract from the fusion with sodium hydroxide and peroxide contains practically all of the osmium and a large part of the ruthenium, as well as minor amounts of iridium. The treatment of the residue that is not dissolved by water is the same as that which has just been described for the separation of iridium.

The alkaline solution of osmium and ruthenium is transferred to a suitable distilling flask, strongly acidified with nitric acid, and then gradually heated to boiling. A current of air is used to carry the vapors of osmium tetroxide into a chain of receiving flasks which contain a solution of sodium hydroxide, roughly 10 per cent. Usually, a small amount of alcohol is added to the solution in the first flask. A solution of ammonium hydroxide and ammonium sulfide may be substituted for sodium hydroxide, in which case the whole solution is evaporated to dryness and the residue ignited under hydrogen to osmium sponge. Some sulfur, however, is retained by the metal.

When no more osmium tetroxide distils, as may be observed by putting a fresh solution in the first receiving flask, the contents of the several flasks are combined and digested to insure the reduction of all osmium tetroxide to sodium osmate. More alcohol is added if needed. Practically all of the osmium may be separated from the ruthenium in this distillation. It has been observed, however, that it is not possible in this way to effect a complete separation of osmium from solutions to which alcohol has been added. In some schemes of refining, osmium is recovered from the alkaline osmate solutions by adding ammonium chloride and

digesting, thus converting the osmium to osmyltetrammine chloride, $[OsO_2-(NH_3)_4]Cl_2$, which can be ignited to metal in an atmosphere of hydrogen. The preparation of pure osmium is discussed in a subsequent section.

After cooling the solution in the distilling flask, it is made strongly alkaline with sodium hydroxide. The solution is then saturated with chlorine, thereby converting ruthenium to the tetroxide, which distils readily when the temperature is raised to 80° or 90°C. The current of chlorine is continued during the distillation but is greatly diluted with air. The receiving flasks in this case contain hydrochloric acid diluted with four volumes of water. A small amount of alcohol is added to each receiver except the first one. When the quantity of ruthenium distilling over decreases, the solution is boiled gently and the distillation continued as long as oily droplets of ruthenium tetroxide appear in the delivery tube. Then more sodium hydroxide is added and the solution again saturated with chlorine, whereupon more ruthenium is distilled. When very little ruthenium tetroxide is obtained on repeated distillation, the remaining iridium, ruthenium, etc. are precipitated by adding a small quantity of alcohol to the neutralized solution from the distilling flask, and boiling. The contents of the receiving flasks are combined and digested to complete the reduction of ruthenium tetroxide, more alcohol being added if needed. The resulting solution is evaporated and set aside for further refining, or ruthenium may be precipitated with ammonium chloride, as described in the section dealing with the purification of this metal. In commercial processes, the evaporated solution is ignited to metal in hydrogen.

2. Operations at the Acton Refinery

The presence of relatively large quantities of platinum metals in the Canadian ores was realized for many years, and when the carbonyl process for the extraction of nickel was first introduced, at Clydach, by the Mond Nickel Company, steps were taken to recover these metals from the rich concentrates produced. In the early days these concentrates were sent to independent refineries for treatment, but later, when the production of nickel had become sufficiently large, the development of a special process and the construction of a special plant for the recovery of platinum metals became economically possible. The methods of refining initiated at the conclusion of the World War formed the basis of the operations conducted in the refinery which was built at Acton (London, N.W. 10) in 1924.

Later, in addition to the concentrates from the carbonyl process, crude platinum from South Africa was also treated. More recently, the treatment of concentrates from the electrolytic nickel refinery at Port Colborne, Ontario, has been undertaken at Acton. The Acton Refinery of the Mond Nickel Company is the largest platinum metals refinery in the world.

Johnson and Atkinson (795) have described the operations carried on at the Acton Refinery. The residues from the Clydach refinery, which contain about 4 per cent of platinum metals in addition to silver and gold, require further concentration before the platinum can be extracted economically with aqua regia.

The refining of the richer concentrates from the nickel and copper refineries, which contain more than 50 per cent of platinum metals and very little silver, commences with the treatment with aqua regia.

For further concentration, the residues containing 4 per cent of platinum metals are smelted with litharge, fluxes, and charcoal in small tilting furnaces, with basic linings, to collect the precious metals and at the same time to slag off silica and base metals. The principal reaction during smelting is the reduction of lead oxide to metallic lead, which acts as a collector of the precious metals. Another important reaction is the conversion of lead sulfate, which forms approximately 50 per cent of the Clydach residue, to lead carbonate by means of sodium carbonate. The lead carbonate immediately decomposes into lead oxide and carbon dioxide. The sodium sulfate separates in the molds as a top slag, which is removed and leached. Subsequent cupellation of the ingots in smaller furnaces removes the excess of lead as litharge, which is used again in further smelting charges, and yields a precious-metal alloy about five times as rich in silver as the Clydach residue. If lead alloys are cupelled to a finish, that is, until litharge ceases to form, there is a probability of producing a cupelled metal which is not readily attacked in the course of subsequent refining operations, hence the reason for partial cupellation.

The alloy formed on cupellation is treated with boiling concentrated sulfuric acid, which removes most of the silver and about one-third of the palladium as sulfates. The residue contains the platinum, gold, and the rest of the palladium in a form particularly suitable for extraction with aqua regia, which is the next operation. From the solution of chlorides thus obtained, the gold is precipitated by ferrous sulfate, and then the platinum as ammonium chloroplatinate by the addition of ammonium chloride, and lastly, the palladium is precipitated as dichlorodiamminepalladium. The only one of these operations which calls for special comment is the precipitation of dichlorodiamminepalladium. The palladium chloride is converted into soluble tetramminepalladous chloride, $[Pd(NH_3)_4]Cl_2$, by the addition of excess ammonium hydroxide. Upon acidification with hydrochloric acid, the sparingly soluble yellow dichlorodiamminepalladium, $[Pd(NH_3)_2Cl_2]$, is precipitated. The impure salt is purified by dissolving it in ammonium hydroxide and reprecipitating it with hydrochloric acid. The salt thus purified is ignited to metallic sponge. The impure ammonium chloroplatinate which is first obtained is ignited to metal, redissolved in aqua regia, and reprecipitated. Ignition of this salt yields platinum sponge. The silver and gold are purified electrolytically, by the Moebius and Wohlwill processes, respectively, special attention being given to the recovery of small amounts of platinum metals.

All liquors resulting from the processes are treated with zinc, or iron, and acid to recover traces of the precious metals. In practice, it is found to be more economical to smelt the final insoluble and reduction residues than to attempt to recover rhodium, ruthenium, and iridium from them by wet processes. The lead ingots obtained by smelting are cupelled to remove excess lead, and the resulting precious metal alloy is parted with nitric acid. The solution is treated

in order to recover precious metals, especially palladium, platinum, and silver, which dissolve during the operation. Most of the rhodium, ruthenium, and iridium initially in the lead alloy are concentrated in the insoluble residue, from which they can be extracted and refined by chemical processes. Rhodium is extracted by fusing the concentrate with sodium bisulfate. Subsequently, the rhodium is refined by a modification of the process described by Wichers, Gilchrist, and Swanger (747). The insoluble residue from the bisulfate fusion is given appropriate treatments to remove platinum, gold, and lead sulfate, as a result of which a concentrate of ruthenium and iridium is obtained. This concentrate is fused with caustic potash and potassium nitrate in spun-iron bowls at a dull red heat, which converts the ruthenium into soluble potassium ruthenate. The cakes are then dissolved in water; after settling, the clear solution is decanted into glass flasks and treated with chlorine. The tetroxide of ruthenium which is formed is absorbed in diluted hydrochloric acid containing methyl alcohol. Evaporation of the contents of the absorption vessels gives an oxychloride, $RuOCl_2$, which is reduced to metal by igniting in hydrogen.

There appears to be very little osmium in the precious-metal concentrates received from the nickel refineries. It amounts to less than 1 per cent of the ruthenium content, and on account of the similarity in properties of these two metals it will be found as an impurity in the ruthenium unless it is eliminated, which can easily be done by heating the ruthenium oxychloride to dull redness in a current of air. The resulting osmium tetroxide is absorbed in an alcoholic caustic soda solution and the osmium finally recovered as osmyltetrammine chloride, $[OsO_2(NH_3)_4]Cl_2$, which can be ignited to metal in an atmosphere of hydrogen.

The caustic fusion, besides converting the ruthenium into potassium ruthenate, which is soluble in water, also converts the iridium into an oxidized form which, although insoluble in water, is dissolved in aqua regia. The chloride solution thus obtained is evaporated, and a crude ammonium chloroiridate obtained by adding ammonium chloride and oxidizing with small amounts of nitric acid. The crude salt is separated from the accompanying ammonium chloroplatinate by fractional crystallization; the use of a mild reducing agent facilitates the solution of the iridium salt. Recrystallization is continued until the desired purity is achieved; the salt is then decomposed by heating in a gas-fired muffle furnace. The partially oxidized metal is reduced by heating in hydrogen and is further purified.

The average purities of the metals recovered from the crude concentrates from the refining of nickel are as follows: platinum, 99.93 per cent; palladium, 99.94 per cent; iridium, 99.7 per cent; rhodium, 99.7 per cent; ruthenium, 99.7 per cent; gold, 99.97 per cent; and silver, 99.97 per cent. In practice, not more than 0.25 per cent of the platinum metals contained in the concentrates is lost, while 1.25 per cent is temporarily retained in furnace slags, which are returned to the nickel refinery for retreatment. The remaining 98.5 per cent is produced directly as refined metal. The losses occurring in the processes of extracting the nickel and copper are also very small, and it is estimated that 90 per cent of the precious metals, probably excepting osmium, contained in the ore is ultimately recovered.

In the wet-process plant of the Acton Refinery chemical stoneware is the material most generally used for the construction of vessels for refining processes involving the use of acids, the two principal types of vessels being mixers or vats up to 100 gallons capacity, and vacuum filters up to 80 gallons capacity.

Aqua regia treatment of concentrates is normally conducted in steam-heated chemical stoneware vessels, each of 140 liters capacity. A temperature of 90°C. is readily obtained, which is adequate for dissolving the finely divided platinum, palladium, and gold contained in the residues. Working under these conditions, there is a further advantage that there is no risk of bumping when heavy insoluble matter settles to the bottom of the vessel. On the other hand, the conditions are quite different for dissolving mineral platinum, which is best done in gas-heated Vitreosil bottles of 70 liters capacity, using concentrated aqua regia at or near the boiling point. Evaporation of nitric acid solutions is done in similar Vitreosil bottles equipped with condensers suitable for the distillation of mineral acids.

Nitric acid treatment is carried out in gas-heated 20-liter basins made of Vitreosil, which are also used for bisulfate fusions. Sulfuric acid treatment is done in pans made of fine-grained gray cast iron, each of 25 liters capacity, and heated by gas. Both lead-lined wood tanks and iron vessels are used for liquors containing free sulfuric acid.

Wooden tanks up to 300 gallons capacity, lined with soft rubber, are satisfactory for some of the operations, for instance, reactions in which sufficient free hydrochloric acid is present to make lead-lined vessels unsuitable. Acid-resisting hose is used to convey acid liquors and to make connections for removing fumes from reaction vessels. Steel vessels lined with hard rubber are preferred to chemical stoneware vessels for operations involving the use of hydrochloric acid in which the heat of reaction causes a rapid rise of temperature. Porcelain ware is used for small-scale purification work.

Decomposition of ammonium chloroplatinate, at the rate of 50 kg. a day, is accomplished in Vitreosil trays which are slowly heated in muffle furnaces fired by gas. Particular care must be taken while heating the material from 310° to 370°C., after which the temperature is raised to 900°C. to complete the removal of volatile matter. Dichlorodiamminepalladium is decomposed in a similar way. The fumes evolved from the decomposing salts are drawn away through a Cronite tube (an alloy containing nickel, chromium, and iron) into a sublimate box, care being taken that the tube does not become choked with condensing ammonium chloride.

The principal feature of the wet-process plant is that the vessels are arranged on terraces. Successive steps of a process can be arranged in a line from top to bottom with gravity flow of the liquor from one vessel to the next.

D. METHODS USED AT THE NATIONAL BUREAU OF STANDARDS FOR THE PURIFICATION OF THE PLATINUM METALS

The preparation of the platinum metals in a highly pure form suitable for the determination of various physical properties, etc., requires description additional to that given for the production of metals of commercial purity. An early phase

of the work on the platinum metals at the National Bureau of Standards, at a time when neither the highly pure metals nor information concerning their preparation was available, was the development of methods for preparing the metals in a degree of purity adequate for the most exacting requirements. These methods are given in condensed form in the following paragraphs. For details the original publications (747, 754, 757) should be consulted.

1. Platinum

(a) By repeated precipitation as ammonium chloroplatinate

Of the methods that have been used for the purification of platinum, repeated precipitation of ammonium chloroplatinate has been the most important and the most widely used. The salt is relatively insoluble. It may be readily precipitated in a form that is easily filtered and washed, and it may be directly converted to metallic platinum by ignition. Any desired degree of purity may be attained by a sufficient number of reprecipitations. However, the number of precipitations required to produce a very pure metal, such as that used for thermocouples and resistance thermometers, is somewhat surprising. It might be expected that in this, as in other processes of purification by recrystallization, the principal cause of difficulty would be the formation of other salts which are isomorphous with that of platinum, especially if they are of the same order of solubility. It is true that all of the other metals except rhodium can exist in the quadrivalent state and in this condition form relatively insoluble salts analogous to ammonium chloroplatinate and isomorphous with it. However, because of the usual course of previous separations, osmium and ruthenium are seldom present with platinum except in very small amounts. Palladium is readily reduced from the quadrivalent to the bivalent state by heating the solution. It is probably true that iridium also is reduced in part, at least, from the quadrivalent state to the tervalent state by heating, especially if the temperature reaches 140–150°C. The ammonium salts of the chloro acids of bivalent palladium and tervalent iridium are much more soluble than ammonium chloroplatinate and not isomorphous with it.

With the possible exception of iridium, therefore, one might expect to eliminate the metals of the platinum group about as rapidly as gold and the base metals, by repeated precipitation of ammonium chloroplatinate. This is not the case. Rhodium, iridium, and palladium display remarkable persistence in contaminating the platinum salt, and rhodium is about as tenacious in this respect as iridium.

Silver may persist through several steps of purification because of the solubility of silver chloride in strong chloride solutions. Part of the dissolved silver chloride is carried down with the precipitate of ammonium chloroplatinate, only to redissolve with the platinum when the sponge is treated with aqua regia. However, experience indicates that silver and gold as well as base metals are usually eliminated before the last traces of platinum metals disappear.

In general, the procedure for preparing pure platinum by repeated precipitation of ammonium chloroplatinate has been as follows: The crude sponge is

dissolved in aqua regia in a porcelain dish provided with a cover glass to prevent loss by spraying. For 100 g. of metal, 300 to 350 ml. of hydrochloric acid (sp.gr. 1.18), 75 to 100 ml. of water, and 60 to 70 ml. of nitric acid (sp.gr. 1.42) are used. The temperature is raised rather slowly to avoid too vigorous a reaction. In some cases more aqua regia is required for complete solution. The solution is evaporated fairly rapidly without previous filtration until the temperature reaches 140–150°C., unless the residue becomes pasty before this temperature is reached, in which case the evaporation must be stopped to avoid local over-heating. If the sponge contained no large amount of base metal or alkali salt, the solution will be fluid at 150°C. A small amount of water is then added, which causes a lively boiling and the evolution of nitrous fumes. More water is added to cool the solution below 100°C. After digestion for a few minutes, some hydrochloric acid is added and the evaporation repeated.

This whole process can be repeated three or four times in a short while, insuring the elimination of nitrous compounds and no doubt promoting the reduction of quadrivalent iridium to the tervalent state. After the last evaporation water only is added and the solution diluted so as to contain not less than 50 and not more than 100 g. of platinum in 1 liter. It is set aside to allow settling of insoluble matter and then decanted or filtered from any residue. The residue may contain undissolved iridium or rhodium as well as silver chloride, silica, and other insoluble matter.

The solution is heated nearly to boiling and treated with a 20 per cent solution of ammonium chloride, using 55 to 60 g. of the salt for each 100 g. of platinum and adding enough in excess so that the whole solution will contain 3 to 5 per cent of the salt. A moderate excess of ammonium chloride is desirable to decrease the solubility of the platinum salt, but a large excess increases the degree of contamination too greatly. The solution is cooled rapidly, and the platinum salt immediately filtered off and drained by suction. If the solution is allowed to stand, a small amount of ammonium chloroplatinate of lower purity will separate and thus contaminate the main precipitate. The salt is drained well, returned to the dish, and thoroughly mixed with a wash solution containing 20 per cent of ammonium chloride. After draining the salt, this whole process of washing is repeated once more. The salt is dried and ignited to sponge. The filtrates and washings are evaporated to recover most of the residual platinum in a second crop of ammonium chloroplatinate, less pure than the first, and for the recovery of other precious metals by precipitation with zinc.

In dealing with very pure platinum, suitable precautions must be taken with the containers and the manner of heating, to avoid contamination of the metal during ignition of the salt. In the laboratory of the National Bureau of Standards ordinary porcelain ware has often been used, as well as some special procelain with a glaze of high softening point. Metal vapors from windings in electrically heated furnaces are to be avoided, if very pure sponge is desired. This can be done by using a glazed muffle or other glazed lining between the heating element and the vessel containing the sponge. When possible, it is desirable to bring about the decomposition of the salt in a reducing atmosphere, preferably

hydrogen. If ammonium chloroplatinate is ignited in the air, there is always some loss of platinum, probably caused by the volatilization of platinous chloride. After the salt is decomposed, the ignition is continued in air. If it is desired simply to prepare the sponge for another step in the process of purification, it is not necessary to exceed a temperature of 500–600°C. A higher temperature causes the sponge to shrink, which makes it more suitable for melting.

(b) By first removing impurities by collective precipitation

Although reprecipitation with ammonium chloride provides an entirely satisfactory way of preparing platinum in any degree of purity, the method is tedious and time-consuming. By first removing impurities by collective precipitation of hydrated oxides, considerable time can be saved.

By the use of this method of removing impurities, and subsequent precipitation of the platinum once with ammonium chloride and ignition to sponge, platinum of an estimated purity of 99.99 per cent was prepared from scrap platinum containing 5 to 10 per cent of impurities, principally platinum metals. From scrap containing 99 per cent of platinum, metal estimated to be 99.995 per cent pure was obtained. Under less favorable conditions metal estimated to be from 99.95 to 99.97 per cent pure was obtained from Colombian grain platinum containing about 84 per cent of platinum, 3 per cent of gold, 8 per cent of iron, 3 per cent of iridium, palladium, and rhodium combined, and 1 per cent of silver and copper. Most of the gold had been removed first by a preliminary treatment of the ore with cold aqua regia.

The procedure used is as follows: The solution of impure platinum in aqua regia is evaporated once or twice to eliminate nitric acid in the manner previously described. Enough sodium chloride is added to form sodium chloroplatinate and similar salts of the other metals. The solution is evaporated and the residue thoroughly dried to remove as much of the hydrochloric acid as possible. The residue is dissolved in water and the solution diluted so as to contain about 50 g. of platinum in 1 liter. If gold is thought to be present, ferrous sulfate solution is added in small portions until no further precipitation of gold occurs. The solution is decanted from the residue and heated nearly to boiling, after which sodium bicarbonate is added in small portions to neutralize most of the remaining hydrochloric acid. When the solution is nearly neutral, as may be judged by diminishing effervescence, 10 to 12 g. of sodium bromate for each 100 g. of platinum is added, only a little being added at first to determine whether the solution is nearly enough neutral not to decompose the bromate. If bromine is evolved, more sodium bicarbonate is added until the addition of a little sodium bromate causes no further evolution of bromine. The remaining sodium bromate is then added, and the addition of small portions of sodium bicarbonate is continued until the solution just turns sensitive litmus paper blue. The solution is now brought rapidly to boiling and again tested with litmus paper. If it is acid, a little more sodium bicarbonate is added and the solution is then boiled for 3 to 5 min. It is finally tested once more; if it is not alkaline, another small portion of sodium bicarbonate is added and the boiling continued for a minute. The solution is then cooled rapidly in running water. Normally, the precipitate

of hydrated oxides settles rapidly, after which the supernatant solution is si-phoned off and passed through a filter to collect suspended precipitate.

The solution containing the platinum is digested with hydrochloric acid to decompose the bromate, and the platinum is precipitated with ammonium chloride. The ammonium chloroplatinate precipitated from this solution will carry down considerable sodium chloride, most of which may be removed by leaching with water after the salt has been ignited to sponge. The precipitate, which consists of the hydrated oxides of palladium, rhodium, iridium, and base metals, obtained by the treatment with sodium bicarbonate, is dissolved in hy-drochloric acid. The solution is worked over for precious metals. More or less platinum will be present, depending on the size of the precipitate and other con-ditions, but the amount should rarely exceed 5 per cent of the platinum in the solution.

2. Palladium

Palladium is perhaps the most simply purified metal of the group. As previ-ously mentioned, commercial refining practice makes use of the property pos-sessed by dichlorodiamminepalladium, $[Pd(NH_3)_2Cl_2]$, of dissolving in ammonium hydroxide and by reprecipitating when the solution is acidified with hydrochloric acid. With the necessary filtrations, and by repeating the operation, palladium of a high degree of purity can be prepared.

If, however, palladium of the very highest purity is to be prepared, it is prob-ably desirable to follow the several reprecipitations of dichlorodiamminepalla-dium by one or more precipitations as ammonium chloropalladate, $(NH_4)_2[PdCl_6]$. If this is to be done, the yellow dichlorodiamminepalladium is dried and ignited to sponge in an atmosphere of hydrogen. The sponge is dissolved in aqua regia and the excess of acid eliminated by evaporation. The residue is diluted and filtered to remove silica or other insoluble matter which may have been introduced by the previous operations involving ammoniacal solutions. The volume of the solution is adjusted to contain 100 g. or more of palladium in 1 liter. An equal volume of saturated ammonium chloride solution and one-third as much nitric acid (sp.gr. 1.42) are added, and the whole solution is then digested in a covered dish on the steam bath until the palladium is precipitated as the crystalline red salt, ammonium chloropalladate. The precipitation can be made so nearly complete as to leave a mother liquor which is almost colorless. The salt is filtered off on a Büchner funnel and washed with a 20 per cent solution of ammonium chloride. If a second precipitation is to be made, the salt is ig-nited to sponge and redissolved in aqua regia. As was previously mentioned, this method of purification, that is, by repeated precipitation with ammonium chloride, aids in the removal of base-metal impurities, particularly those which remain dissolved in an ammoniacal solution, but it does not tend to eliminate the other platinum metals rapidly.

3. Rhodium

Of the six platinum metals, rhodium and iridium are the most difficult to pre-pare in the highest degree of purity. The following description is that of the

procedure used to prepare rhodium for measurement of its freezing point (757), and to a considerable extent it supersedes that given in an earlier publication (747). Since this earlier publication further experience has shown that the repeated precipitation of ammonium rhodium nitrite, although very effective for removing other impurities, is not satisfactory for removing more than very small amounts of iridium. In order to reduce the iridium content of the rhodium to an amount suitable for the application of the nitrite process, the following method was used for dissolving the rhodium.

The impure rhodium was mixed with about twenty parts of lead, and the mixture was fused in a graphite crucible at about 1000°C. for half an hour. Although it might sometimes be disadvantageous to add lead to rhodium, because of the difficulty of eliminating all of it in the subsequent process of purification, it is usually of no consequence, because lead is very often an impurity in rhodium. The resulting alloy was treated with nitric acid to dissolve most of the lead. In this treatment a little rhodium dissolved, but most of it was left as a finely divided alloy with lead. This alloy was vigorously attacked, first with concentrated hydrochloric acid, and then with aqua regia, leaving finally a residue which contained nearly all of the iridium, together with a small portion of the rhodium.

Most of the lead was precipitated from the acid solutions with sulfuric acid, added in slight excess. The filtrates from the lead sulfate were combined and evaporated to a small volume to expel most of the free acids and to obtain a second precipitate of lead sulfate. The filtrate from this precipitate was treated with a sufficient amount of a solution of sodium nitrite to neutralize the remaining free acid and to convert the rhodium chloride into sodium rhodium nitrite, $Na_3[Rh(NO_2)_6]$. The solution was boiled to complete the conversion to nitrite. To this solution, which contained about 50 g. of rhodium in 1 liter, was added about 30 g. of sodium sulfide crystals for each 100 g. of rhodium. This was done to precipitate certain base-metal impurities, such as copper and lead. Some of the platinum-metal impurities, especially palladium, are partially precipitated by this treatment, but very little of the rhodium is lost. After standing overnight, the sulfide precipitate was filtered off and the solution boiled to consume any remaining sodium sulfide by its reaction with platinum-metal impurities or with the rhodium itself. After removal of the second small precipitate of sulfides, the solution was cooled to about 15°C. and treated with a solution of ammonium chloride to precipitate a salt which has generally been regarded as $(NH_4)_3[Rh(NO_2)_6]$ but which may be a mixed sodium and ammonium rhodium nitrite. About 200 g. of ammonium chloride was used for each 100 g. of rhodium. This proportion includes a small excess of ammonium chloride, which decreases the solubility of the double salt.

After filtering and washing the salt, it was decomposed with hydrochloric acid diluted with three or four volumes of water. The chloride solution was then evaporated to expel most of the hydrochloric acid and the cycle of operations with sodium nitrite, sodium sulfide, and ammonium chloride repeated six times. The quantity of sodium sulfide used was decreased each time, and the sulfide precipitates were examined chemically for lead. Lead was not detected after

the fourth precipitation. At this stage a solution of sodium nitrite which had been treated to remove traces of base metals was substituted for the ordinary reagent.

Spectrochemical examination of the rhodium from the fifth precipitation failed to disclose the presence of any other platinum metals, but indicated a trace of lead. Lead was not found in the metal from the sixth precipitation. The salt obtained by the seventh precipitation was converted into a chloride solution, by means of hydrochloric acid, and ammonium chloride was added in slight excess of the amount equivalent to $(NH_4)_3[RhCl_6]$. The ammonium chlororhodate was then precipitated from this solution, which contained about 100 g. of rhodium in 1 liter, by adding 1.5 times its volume of 95 per cent alcohol. The salt was washed with alcohol, dissolved in water, and reprecipitated by means of alcohol from a somewhat more dilute solution. The salt thus prepared contained, after drying, 30.7 per cent of rhodium.

The salt was ignited in a porcelain container in a resistance furnace in such a way as to prevent contamination with metal vapors from the winding. The residue was reduced to rhodium sponge by ignition in hydrogen, and the sponge digested with water to extract a small amount of alkali salts.

Since the work described above was done, much has been learned about the conditions under which various base metals, including lead, can be precipitated hydrolytically from the nitrite solutions of the platinum metals. In view of this the repeated treatment with sodium sulfide probably could be greatly simplified, if not eliminated.

4. Iridium

The purification of iridium is attended by unusual difficulties. The literature on iridium does not include methods which can be depended upon for the complete elimination of impurities, even though they may be satisfactory for preparing metal of commercial purity.

The following discussion was written concerning the method used to prepare iridium for the measurement of its freezing point (754). Like the description for the preparation of pure rhodium, this for iridium modifies somewhat the one given in an earlier publication (747) of the National Bureau of Standards.

All the base metals ordinarily associated with iridium, as well as silver, gold, and probably palladium, can be removed by precipitating the iridium several times as ammonium chloroiridate, $(NH_4)_2[IrCl_6]$, provided proper precautions are taken. Platinum and ruthenium, on the other hand, cannot be separated from iridium in this way because they form chloro salts of the same order of solubility as the iridium salt. Even rhodium, which does not form an analogous, slightly soluble chloro salt, will contaminate the iridium compound with the utmost persistence, so that it is wholly impracticable, if not impossible, to get rid of rhodium in this way. No difficulty is experienced with osmium, which, although it forms a chloro salt similar to that of iridium, is volatilized as the tetroxide when the solution is digested repeatedly with nitric acid or aqua regia, in the usual refining process.

When iridium is precipitated as ammonium iridium nitrite, platinum and

ruthenium concentrate rapidly in the mother liquors and could probably be completely eliminated by several precipitations of that salt. This procedure can also be adapted to the separation of most of the base metals. However, in this instance it is rhodium which forms an analogous salt, somewhat less soluble than the iridium compound. Hence, rhodium could be eliminated only by a long-continued process of fractional precipitation, which is not very suitable when only a limited amount of material is available, and which in any case is not favorable to the purification of the more soluble of the two salts. Such a method would be better for freeing rhodium of iridium than *vice versa*.

Up to the present time no slightly soluble, easily handled compound of iridium has been thought of which can be repeatedly precipitated and thereby effect the complete removal of rhodium. The earlier work indicated that ruthenium could be eliminated by fractional precipitation with hydrogen sulfide, but that the yield of iridium was not very favorable. Later work has shown that this treatment also gets rid of rhodium and platinum. The poor yield (sometimes only 50 per cent of fairly pure starting material) is offset by the simplicity of the operation and the fact that all three of the most persistent impurities are eliminated together.

Briefly, the procedure followed for the preparation of pure iridium consisted in saturating the acidified chloride solution (50 g. of metal and 50 ml. of concentrated hydrochloric acid in 1 liter was found to give satisfactory conditions of concentration) with hydrogen sulfide at room temperature and keeping it saturated for a week or longer, during which time platinum, rhodium, ruthenium, etc. slowly precipitated, together with a portion of the iridium. The precipitation was stopped when spectrochemical examination of the iridium obtained from the filtered solutions showed no trace of other platinum metals. Foreign metals which were not completely removed by hydrogen sulfide at the prevailing acidity were then eliminated by repeated precipitation of ammonium chloroiridate, sometimes combined with one or more precipitations of ammonium iridium nitrite.

Later work has shown that the yield of iridium, that is, the amount left unprecipitated by the hydrogen sulfide, was greater when a more concentrated solution of iridium was used and its acidity more carefully controlled. When the chloroiridic acid was converted to its sodium salt, and the resulting solution made to contain 100 g. of iridium and 35 ml. of concentrated hydrochloric acid in 1 liter, a yield of over 80 per cent was obtained. Spectrochemical examination of iridium prepared in this way disclosed no platinum-metal impurity except a trace of rhodium. To obtain a good yield, it is necessary to eliminate most of the platinum metals by other methods, before applying the fractional precipitation with hydrogen sulfide.

5. Osmium

Osmium, isolated by distillation as osmium tetroxide and absorbed in sodium hydroxide, may be recovered in a number of ways. The commercial procedure is to form osmyltetrammine chloride, which is ignited in hydrogen to metal.

A simple way is to precipitate hydrated osmium dioxide hydrolytically by neutralizing the solution with hydrochloric or sulfuric acid. By whatever method the osmium is recovered, the reduced metal obtained serves as the starting point for the preparation of pure osmium.

The procedure for preparing pure metal is as follows: Metallic osmium, recovered by any of the methods just mentioned, is heated in boats in a hard-glass tube, using an electric furnace for the purpose. Half of the glass combustion tube is bent downward at an angle of 45° and the end of the tube just submerged in 6 N hydrochloric acid contained in an Erlenmeyer flask. A slow current of oxygen is passed through the tube. At about 220–230°C. a vigorous reaction occurs, accompanied by a rapid absorption of oxygen and a progressive glowing of the metal. The resulting product is a black powder of greater bulk than the metal, and is probably osmium dioxide. At this stage it is necessary to supply oxygen rapidly to avoid a diminished pressure in the tube.

After this reaction subsides, the temperature is raised gradually, whereupon the material in the boats is quietly oxidized to osmium tetroxide. The latter compound condenses to a solid in the cool portion of the tube. When oxidation of the material in the boats is complete, the solidified tetroxide in the tube is loosened by gentle warming and dropped into the flask. It is then quickly transferred to a flask fitted to a reflux condenser by a ground-glass joint. The top of the condenser is fitted with a trap containing sodium hydroxide.

In the reaction flask the osmium tetroxide is gradually converted to chloroosmic acid, $H_2[OsCl_6]$, if hydrochloric acid is used, or to bromoösmic acid, $H_2[OsBr_6]$, if hydrobromic acid is used. A small amount of alcohol aids the reaction with hydrochloric acid, but it is not actually necessary with hydrobromic acid. The flask is warmed gently, and the temperature raised gradually to that of incipient boiling during a period of 3 hr. In the case of hydrochloric acid the reaction may be regarded as complete when the color of the solution changes to a clear transparent red, characteristic of $H_2[OsCl_6]$, and no droplets of condensing tetroxide are observed or the odor of tetroxide detected. At least twice the theoretical amount of hydrochloric acid required to form $H_2[OsCl_6]$ should be used. The reaction with hydrobromic acid is much more rapid than that with hydrochloric acid, and it is to be preferred if large amounts of osmium are being handled.

Solutions of chloroösmic acid are stable and do not decompose or lose osmium on evaporation if the acid concentration is at least 2.8 N. Ammonium chloride precipitates brick-red ammonium chloroösmate, $(NH_4)_2[OsCl_6]$, from solutions of the chloro acid; and ammonium bromide precipitates brownish black ammonium bromoösmate, $(NH_4)_2[OsBr_6]$, from solutions of the bromo acid. Ignition of either of these salts in hydrogen yields osmium sponge, which is cooled in an inert gas such as nitrogen or carbon dioxide.

If metal of the very highest purity is desired, as for the determination of atomic weights, the cycle of operations is repeated, using specially prepared reagents.

6. Ruthenium

Ruthenium, isolated by distillation as ruthenium tetroxide, is absorbed in hydrochloric acid diluted with four volumes of water. The solution is evaporated on the steam bath to eliminate the excess of hydrochloric acid. The addition of ammonium chloride to a filtered concentrated solution of the chloro acid of ruthenium precipitates a salt, probably $(NH_4)_2[RuCl_5OH]$ or $(NH_4)_2[RuCl_6]$. This salt is filtered on a Büchner funnel and washed with a 20 per cent solution of ammonium chloride. Reduction of the salt in hydrogen produces metallic ruthenium.

VI. Analysis of Platiniferous Materials

To appreciate the advances which have been made during the past twenty years in perfecting methods for analyzing platiniferous materials, it is well first to examine the state of the analytical chemistry of the precious metals at the beginning of the World War.

A. Traditional Methods

Holtz (791), after considering the methods (782, 786, 788, 789, 798) which had been proposed for the analysis of native grain platinum and for platinum alloys, schematic diagrams of which are reproduced in the book published by Duparc and Tikonowitsch (763), attempted to incorporate their various desirable features, together with some of his own devices, into a procedure which he used to analyze native platinum. Holtz' modifications, however, added little to the solution of the riddle of analyzing crude platinum. Two of the methods just cited do deserve attention: namely, that of Deville and Stas for the analysis of platinum alloys, and that of Leidié, which has recently been developed into a procedure for analyzing dental gold alloys (760).

An important contribution made at Geneva was the application by Wunder and Thüringer (812) of Chugaev's dimethylglyoxime to the separation and determination of palladium. The precipitation of palladium by dimethylglyoxime deserves a place in the front rank of analytical reactions. Its very excellence serves to show by contrast how great are the shortcomings of some of the traditional analytical methods for the platinum group.

1. Separation of platinum, palladium, rhodium, and iridium from one another by ammonium chloride

The most common operation in the analysis of platiniferous material has been the precipitation of platinum as ammonium chloroplatinate. This reaction has been generally used to separate platinum from rhodium and palladium and, in some schemes of analysis, from iridium after reducing this metal to the tervalent state. The convenience of this method of separation is so great that the analyst has been prone to ignore its inherent errors. One type of error results from the persistent contamination of the platinum salt by rhodium and iridium, even though these metals be tervalent, and, to a less extent, by palladium. The other error occurs because ammonium chloroplatinate is appreciably soluble.

It is true that the solubility of the platinum salt can be reduced to an amount which may be negligible in some analytical procedures, by adding a large excess of ammonium chloride and digesting the solution. These conditions, however, greatly increase the contamination of the salt by the other platinum metals. It is not at all unusual, for example, if a small amount of rhodium is present, for the familiar orange-yellow compound to turn bright green as the digestion proceeds. The solubility of the platinum salt also deters the careful analyst from reprecipitating it one or more times to purify it. When this is done, the increase in analytical accuracy resulting from the improved separation from the related metals is offset by loss of platinum. The practical consequence is that a determination of platinum which is based on its separation from the other platinum metals by precipitation with ammonium chloride or potassium chloride can be accurate only by the accident of compensating errors.

The shortcomings of the precipitation of ammonium chloroplatinate for analytical purposes were well recognized by such early workers as Deville and Stas. In their excellent work on the analysis of the platinum–iridium alloy used to fabricate the International Prototype Meter, these authors discussed at length the incomplete precipitation of ammonium chloroplatinate and its contamination by other metals, especially rhodium. They showed that the degree of contamination varies with the mode of precipitation. Under the best conditions of separation, the platinum obtained in an analysis of an alloy containing 0.65 per cent of rhodium still contained 0.2 per cent of rhodium. Moreover, a considerable amount of platinum remained in the mother liquor and was recovered with the major part of the rhodium. They quite frankly regarded precipitation with ammonium chloride as a preliminary separation. A further separation was obtained by extracting the rhodium from two or three fractions, obtained by means of ammonium chloride, with molten potassium pyrosulfate. This is at best a laborious operation which must be repeated several times. Furthermore, a portion of the platinum dissolves in the pyrosulfate and not all of the rhodium can be extracted. The method offers a closer approximation to an accurate separation of rhodium from platinum than does the procedure with ammonium chloride alone and reflects credit on the efforts of its authors to determine the, actual rhodium content of the material they examined. Nevertheless, it is much too tedious for routine use and not satisfactory when a high degree of accuracy is necessary.

The separation of iridium from platinum by means of ammonium chloride has the same shortcomings as the separation of rhodium from platinum. In addition, there is the difficulty of reducing all of the iridium to the tervalent state before precipitating the ammonium chloroplatinate. Too vigorous reduction of the mixed chlorides may result in a partial reduction of platinum to the bivalent condition. Frequently, the effort of the analyst has been directed toward keeping both the iridium and platinum in the quadrivalent state and precipitating the two together with ammonium chloride, in the hope of first separating them from rhodium and palladium. The subsequent separation of the iridium and platinum from each other was based on igniting the mixed salt

to sponge and extracting the platinum with diluted aqua regia. Such an extraction cannot yield accurate analytical results, except by the accident of compensating errors, because iridium sponge is not wholly insoluble in aqua regia and because platinum is not completely extractable. Experience also shows that it is even more difficult to get approximately complete precipitation of ammonium chloroiridate than of ammonium chloroplatinate. Furthermore, rhodium is entrained by the iridium salt even more persistently than by the platinum salt. Palladium appears to be more easily separated from platinum by ammonium chloride than is rhodium or iridium. Fortunately, the analyst is now in possession of the organic reagent dimethylglyoxime, and has no further worries with palladium.

The only truly quantitative separation of iridium from platinum which had been developed prior to 1914 is that discovered by Deville and Stas (789) and used by them for the determination of iridium in alloys from which the Prototype Meter was fabricated. In this method the platinum–iridium alloy is melted with about ten times its weight of lead, thus producing alloys of lead and platinum which are soluble in acids, and crystalline iridium which is virtually insoluble in aqua regia. A study of the method at the National Bureau of Standards (742, 743) confirmed its accuracy and led to certain modifications which increase the ease and speed of operation. The method is an excellent one for the routine analysis of platinum alloys which contain no iron or ruthenium (or osmium). In the lead fusion, ruthenium alloys itself quantitatively with the iridium, and iron nearly so. The subsequent removal of ruthenium and iron, to obtain a correct determination of iridium, is laborious. As a method for determining iridium only, in an alloy containing iridium, platinum, rhodium, palladium, gold, and copper, for instance, it stands as a tribute to the ingenuity of its authors.

B. METHODS OF EFFECTING SOLUTION OF PLATINIFEROUS MATERIALS

Relatively few types of reactions are used to effect solution of platiniferous materials. Material which is insoluble in aqua regia, such as osmiridium, metallic iridium, and metallic rhodium, is usually rendered soluble by means of fusion with alkaline oxidizing fluxes, followed by treatment with hydrochloric acid. Mixtures of sodium hydroxide and sodium nitrate or of sodium hydroxide and sodium peroxide are frequently employed. Barium peroxide alone is sometimes used. In these operations it is necessary to use vessels of gold, silver, nickel, or iron. Rhodium is conveniently converted to a soluble form by heating its mixture with sodium chloride in an atmosphere of chlorine.

A method recently developed by Wichers, Schlecht, and Gordon (761, 762) at the National Bureau of Standards deserves particular mention, because it solves one of the most difficult problems of the platinum analyst. They found that refractory platiniferous material could be brought completely into solution by heating it in contact with hydrochloric acid which contains a small amount of a suitable oxidizing agent, in a sealed glass tube at an elevated temperature. The rate of attack varies greatly with the composition of the acid mixture as well as with the temperature. A mixture of twenty volumes of concentrated

hydrochloric acid with one volume of fuming nitric acid, or an equivalent amount of sodium chlorate, perchloric acid, or chlorine, is satisfactory. Such a mixture at a temperature of about 300°C. will dissolve osmiridium and even metallic iridium at a fairly rapid rate. Leaving the tubes in a controlled oven for 24 hr. is sufficient for an average specimen of osmiridium, but large grains or exceptionally refractory specimens may take longer. About 20 ml. of the acid mixture is used for 1 g. of metal. If the samples are as small as 100 mg., heavy-walled glass tubes of 4-mm. bore and about 20 cm. long, half filled with acid, can be heated safely to 300°C. without much danger of bursting. Larger tubes are heated in a steel bomb into which a weighed amount of solid carbon dioxide is put to provide the proper compensating pressure. Pressures within the glass tubes are estimated at 3500 to 4000 pounds per square inch at 300°C.

When the solution of the sample is complete, the tube is chilled in a bath cooled with solid carbon dioxide before it is cut open. This serves to reduce any excess pressure within the tube and to prevent the escape of volatile substances, such as osmium tetroxide. The opened tube is then inverted in a solution of hydrochloric acid containing sulfur dioxide, and allowed to come to room temperature. This effectively prevents loss of osmium tetroxide.

In general the method is advantageous because any type of platiniferous material can be brought into chloride solution without loss of any constituent and without introduction of large amounts of alkali salts. For details concerning the optimum conditions of attack of various materials, a forthcoming paper (762) in the *Journal of Research of the National Bureau of Standards* should be consulted.

C. METHODS OF SEPARATION BASED ON HYDROLYTIC PRECIPITATION

The formation of insoluble hydroxides of the platinum metals is not a newly observed phenomenon. A century ago milk of lime was added to solutions of native platinum in the process of refining at the Russian Mint. Claus (784), the discoverer of ruthenium, did point out that the elimination of impurities by this method was never complete.

In 1914 Mylius and Mazzucchelli (803) used a solution of sodium bicarbonate in bromine water for the collective precipitation of impurities in the approximate analysis of commercial platinum. They did not, however, obtain quite complete separation of the impurities. Somewhat later, Wichers (745), modifying the method of Mylius and Mazzucchelli, developed a hydrolytic procedure for separating rhodium from platinum, and made observations on the behavior of the other platinum metals.

In a series of experimental researches Gilchrist (748, 750, 752, 755, 756) developed a complete system of analysis for the platinum group, in which the method of hydrolytic precipitation was utilized. A discussion of this new method is given in the proceedings of the Ninth International Congress of Pure and Applied Chemistry (758), and of the analytical procedure in the *Journal of the American Chemical Society* (759).

These researches revealed that there were some ranges of hydrogen-ion con-

centration within which the members of the platinum group, with the exception of platinum itself, are completely precipitated by hydrolysis, when in the form of their chloro acids. For osmium the range appears to be about pH 1.5 to 6, with optimum conditions at pH 4; for iridium, pH 4 to 6; while for rhodium and palladium an alkalinity equivalent to pH 6 is the minimum that will insure complete precipitation. For ruthenium the conditions appear to be such that little variation from pH 6 is permissible. Palladium, rhodium, and iridium are most advantageously precipitated in the presence of sodium bromate, and in the complete analytical procedure it is recommended that the neutralization be finally carried to pH 8 to make certain that palladium and rhodium are completely precipitated. This alkalinity has no disturbing effect on the iridium precipitate.

Not all reagents which can furnish the necessary hydroxyl-ion concentration are suitable as neutralizing agents, because some of them,—for example, nitrite, phosphate, and ammonium hydroxide,—convert the chloro compounds of the platinum metals into other types of compounds, rather than into insoluble hydroxides.

The control of the acidity or alkalinity at which the platinum-metal hydroxides are to be precipitated cannot usually be attained by means of an indicator added directly to the solution. Solutions of the platinum metals are highly colored, and the precipitates which form obscure observation of the indicator. Furthermore some of the reagents, such as bromate, destroy the indicators. Nevertheless, it is possible to utilize indicators in a very simple manner. The operation of testing is performed by lifting the stirring rod above the level of the solution and adding a drop of the indicator to the drop which has clung to the end of the rod. The stirring rod is then replaced in the solution, with no loss of material. This method of testing is not that of the usual "outside indicator". The end point determined in this way is practically identical with that determined by adding the indicator directly to the main body of a solution.

The indicators which have proved to be the most useful in controlling hydrolytic precipitations are the sulfonphthalein indicators, in the form of their monosodium salts, at a concentration of 0.01 per cent. These indicators are: thymol blue, which changes from red to orange at about pH 1.5, in the direction from acid to alkaline, and from yellow to blue at about pH 10; brom phenol blue, yellow to blue at pH 4; brom cresol green, yellow to blue at pH 4.7; chlorphenol red, yellow to red at pH 6; brom cresol purple, yellow to blue at pH 6.3; brom thymol blue, yellow to blue at pH 7; cresol red, yellow to pink at about pH 8; and xylenol blue, yellow to blue at an alkalinity slightly greater than pH 8.

D. SEPARATION OF THE PLATINUM METALS FROM ONE ANOTHER

1. Separation of palladium, rhodium, and iridium from platinum, by hydrolysis

The superiority of the hydrolytic method in effecting the separation of platinum from palladium, rhodium, and iridium lies in the fact that the separations

are clean-cut, simple, and quantitative. Palladium, rhodium, and iridium, either singly or collectively, can be separated from platinum. If the separation is effected in the presence of bromate, the hydroxides settle well, are readily filtered, and contain so little platinum that the separation obtained by a single precipitation is superior to that obtained by many commonly used procedures, and needs to be repeated only once to attain strictly quantitative accuracy.

Oxidation of palladium, rhodium, and iridium is readily accomplished by adding a small amount of sodium bromate to the hot, slightly acidified solution prior to neutralization. The addition of bromate has the further advantage that it retards the reaction of the chloroplatinate radical with hydroxyl ions. The way in which it does so is as yet unexplained, but the effect is unmistakable. It is not really necessary, however, to add bromate for the purpose of retarding the hydrolysis of the chloroplatinate radical, because this radical hydrolyzes so slowly at pH 6 and at the concentrations of platinum usually handled in analytical work that there is no interference. In any case, the first stages of the hydrolysis of chloroplatinate do not result in the formation of insoluble compounds. The essential purpose of the bromate is, of course, to insure the oxidation of palladium, rhodium, and iridium to a state of valency higher than that at which they normally exist.

Not long after the accidental death of Ludwig Moser of the Technische Hochschule at Vienna, two of his students, Hackhofer and Graber, reported on the separation of iridium (400) from platinum, and of rhodium (401) from platinum, by a hydrolytic procedure in which the alkalinity of the solution is fixed by the reaction between bromate and bromide ions. This reaction, however, appears to come to equilibrium so slowly that prolonged boiling and digestion are required to complete the precipitation. In the case of iridium, particularly, the hydrolytic product which is formed is very difficultly soluble. In their procedures, these authors make no provision for repeated precipitation to eliminate platinum completely.

2. Isolation of palladium

Wunder and Thüringer, in precipitating palladium with dimethylglyoxime in the presence of platinum in a hot solution, encountered difficulty in effecting the separation. The cause of this difficulty lies in the reduction of some of the platinum from the quadrivalent to the bivalent state. Like palladium, which is bivalent, bivalent platinum also forms the same kind of inner complex salt with dimethylglyoxime. To avoid this difficulty, Wunder and Thüringer, in their procedure (812) for the isolation of palladium in the analysis of native platinum, recommend that the platinum and iridium be removed first, by precipitation with ammonium chloride. The palladium (together with gold) is then precipitated from the boiling filtrate by adding dimethylglyoxime.

It remained for Davis (712) to point out that the coprecipitation of platinum which occurs in a hot solution can be avoided by operating at room temperature, and that the results thus obtained are very satisfactory if the palladium is reprecipitated, even though the original ratio of platinum to palladium happens

to be large. Swanger (746), in his development of a procedure for the analysis of dental gold alloys, confirmed the experience of Davis.

The precipitation of palladium in the presence of platinum can be made and is recommended in certain instances, provided it is performed in cold solution and the precipitate is not allowed to remain too long before being removed by filtration. Swanger performed the second precipitation of palladium, in its separation from platinum, by decomposing the glyoxime precipitate first obtained with nitric acid or aqua regia, diluting the solution, and adding more glyoxime. If this is done, it should be borne in mind that a small amount of palladium may remain in solution. It is not apparent why this should occur unless, perhaps, a small amount of the palladium exists as a nitroso compound which does not react with the glyoxime.

The ideal conditions for the application of dimethylglyoxime to the isolation of palladium, in the analysis of platiniferous materials, exist when the platinum has first been completely removed. The hydrolytic method of treatment accomplishes the removal of platinum simply and efficiently. With platinum completely eliminated, the problem of isolating palladium with dimethylglyoxime is greatly simplified. With the amounts of palladium, rhodium, and iridium ordinarily handled analytically, a single precipitation of palladium by dimethylglyoxime separates this metal from rhodium and iridium without contamination. The precipitation is best made in a solution of these three metals as chlorides or sulfates, to which forms the hydrated oxides are readily converted. If the amount of iridium is large, and the iridium has been converted to the blue form of its sulfate by fuming with sulfuric acid to which nitric acid has been added, some trouble may be encountered. It was observed that under such circumstances the glyoxime precipitate seemed finely divided and a colloidal substance tended to pass through the filter. If, however, the iridium is entirely in the tervalent state, as is also the rhodium under all conditions, no interference occurs. A theoretical explanation of the reason why rhodium and iridium do not contaminate the precipitate of palladium with dimethylglyoxime is considered in Section VIII.

3. Separation of rhodium and iridium from each other

The separation of rhodium from iridium has long been one of the most difficult of the analytical problems of the platinum group of metals. Berzelius (782), in a general scheme for the analysis of crude platinum, used molten potassium bisulfate to separate these two metals from each other. This method is unsatisfactory because of the incomplete removal of rhodium and the partial solution of iridium. The separation of rhodium from iridium by ammonium chloride has already been discussed.

As previously mentioned, Deville and Stas (789) had discovered a reaction, involving fusion with lead, whereby iridium could be isolated, and, under certain restrictions, a method based on this reaction effects the quantitative separation of iridium from rhodium. The recovery and isolation of rhodium, however, are another matter. Wöhler and Metz (263) in 1925 substituted bismuth for lead

in the procedure of Deville and Stas, as did also Karpov (204) in 1928. More recently it was found possible to effect a strictly quantitative separation of these two metals from each other, and to recover each one for determination. The method (752) by which this was accomplished had its origin in the observation by Wada and Nakazono (682) in 1923 that rhodium is precipitated by the reducing action of titanous sulfate while iridium is not, if the chloride solution of each metal is treated separately. The procedure that Wada and Nakazono described for the separation of rhodium from iridium was apparently not intended to be a quantitative one. Its method of presentation is entirely that of a qualitative procedure. No provision is made for dissolving the precipitated metallic rhodium, in order that it can be reprecipitated to free it of iridium which, under the conditions of their treatment, is partially precipitated.

The successful development of Wada and Nakazono's idea came about through the ability to redissolve the metallic rhodium in boiling sulfuric acid; thus the rhodium could be reprecipitated. It was found that less contamination of the rhodium by iridium occurred if the precipitations were made in a solution containing the two metals as sulfates. Since the second precipitation had to be made in sulfate solution, there was no reason why the first should not be done so too. With the quantities of rhodium and iridium usually handled analytically, two precipitations of the rhodium as metal suffice to effect quantitative separation. Since a 20 per cent solution of titanous chloride can be purchased, this reagent is recommended.

When the operation is over, the analyst is confronted with the problem of removing the considerable quantity of titanium which has been added. Fortunately, the organic reagent, the ammonium salt of nitrosophenylhydroxylamine, $C_6H_5N(NO)ONH_4$, ordinarily referred to as cupferron, precipitates quadrivalent titanium in either hydrochloric or sulfuric acid solution. Cupferron also acts as a scavenger. It precipitates a number of other elements beside titanium, notably iron. The iridium is finally recovered by hydrolytic precipitation of its hydrated dioxide.

Karpov and Fedorova (205) in 1933 proposed a method for the separation of rhodium from iridium in which a solution of these metals in strong hydrochloric acid is treated in the cold with mercuric chloride and vanadium dichloride, VCl_2. According to the authors the iridium is reduced to the tervalent state, while the rhodium is reduced to metal and forms an amalgam. They claim that unless the rhodium forms an amalgam it is difficult to redissolve it, and since iridium usually contaminates the precipitate, reprecipitation is necessary. The rhodium amalgam is dissolved in aqua regia, the solution is evaporated, and the residue is heated to drive off mercuric chloride. The resulting residue is dissolved in hydrochloric acid and the precipitation of rhodium is repeated. A third and final precipitation is made without adding mercuric chloride. The rhodium so obtained is ignited, treated with hydrofluoric acid and with hydrochloric acid to remove traces of silica, iron, and zinc, reduced in hydrogen, and weighed. No provision is made for the separation of iridium from vanadium or for its recovery.

4. Isolation of osmium

Distillation of the tetroxide of osmium, usually from a solution acidified with nitric acid, has been universally used to separate this element from the other platinum metals. Despite the general use of this process, no study seems to have been made of the completeness of the separation or of the best operating conditions until 1931, when an investigation of the separation and determination of osmium (750) was undertaken at the National Bureau of Standards.

In this study it was found that the form in which the osmium exists in solution has a marked effect on the speed with which it is eliminated. If it is in the form which results when an osmium-bearing material is fused with alkaline reagents, such as sodium hydroxide and sodium peroxide or nitrate, it is eliminated completely in about 1 hr. from a boiling solution which contains at least 10 per cent of its volume of free nitric acid of specific gravity 1.4. The same thing is true if the osmium exists as bromoösmate, but if it is in the form of chloroösmate as much as 8 hr. may be required to complete the distillation. In the latter case it is better, if possible, to distil from concentrated sulfuric acid. Under these conditions osmium is quickly separated as the tetroxide. (Strangely enough, on the other hand, if the osmium exists as the bromoösmate it is eliminated very slowly from boiling concentrated sulfuric acid.) The addition of a small amount of nitric acid to the sulfuric acid solution further expedites the elimination of osmium. However, nitric acid should not be added to the sulfuric acid unless ruthenium is known to be absent, since ruthenium tetroxide is slowly formed under these conditions. In the absence of nitric acid ruthenium tetroxide is not formed in the boiling concentrated sulfuric acid, and the separation of osmium from ruthenium, as well as from the other metals, is complete. The separation of osmium is also complete when the osmium tetroxide is distilled from a nitric acid solution (containing little or no sulfuric acid), if the concentration of nitric acid does not exceed about 40 per cent. A complete separation of osmium from the other platinum metals is thus found to be possible by the traditional method, if proper precautions are observed.

5. Isolation of ruthenium

The traditional method for separating ruthenium from the other platinum metals, except osmium, is to saturate an alkaline solution of the metal with chlorine, and to remove by distillation the ruthenium tetroxide thus formed. Everyone familiar with this method knows that the process of adding fresh alkali, saturating with chlorine, and distilling must be repeated several times, if even an approximately complete elimination of ruthenium is to be achieved. The cause of the incomplete elimination of ruthenium in this process probably lies in the entrainment of ruthenium by the precipitates of iridium or other hydroxides which are formed when the alkaline solution of sodium hypochlorite is changed to a nearly neutral solution of sodium chlorate, by heating. It has been observed that the precipitate of iridium which is produced under these conditions catalytically decomposes chlorate and bromate with the production of oxygen.

To avoid the difficulty encountered in eliminating ruthenium from an alkaline solution by means of chlorine, a procedure (755) was developed at the National Bureau of Standards by which ruthenium tetroxide is distilled from a solution sufficiently acid to prevent the precipitation of iridium. It was found that bromic acid, produced by adding sodium bromate to a solution containing about 5 ml. of free sulfuric acid of specific gravity 1.84 in 100 ml., will oxidize ruthenium to its tetroxide and permit its complete removal by distillation. The best conditions obtain if the ruthenium has first been converted to ruthenium sulfate. If the ruthenium exists as the chloride, the distilling operation will require about 4 hr.; if it is in the form of sulfate, only 2 hr. are required. The presence of the other platinum metals in the solution, or even of finely divided platinum which is formed during the conversion of chlororuthenate to ruthenium sulfate by fuming with sulfuric acid, does not interfere with the complete elimination of ruthenium tetroxide. The conversion of the ruthenium to its sulfate, prior to distillation, has the advantage of eliminating chlorides. If present, chlorides appear to cause a trace of ruthenium, probably in the form of the dioxide, to deposit on the glass surface near the top of the distilling flask. This deposit is not readily removed.

6. Recovery and determination of the platinum metals

A very suitable reagent in which to absorb quantitatively osmium tetroxide, and also ruthenium tetroxide, consists of 6 N hydrochloric acid which is saturated with sulfur dioxide. This reagent reduces these tetroxides and forms chloroösmic acid and chlororuthenic acid, respectively. From the evaporated solutions, after destruction of sulfito complexes, osmium and ruthenium, respectively, are precipitated as hydrated oxides. That of osmium cannot be caught on filter paper, as are the precipitates of the other five platinum metals, and ignited in air. It is best caught in a platinum filtering crucible which has a filtering pad of platinum sponge, known as a Munroe or Neubauer crucible. The precipitate is ignited in hydrogen, the hydrogen is displaced by carbon dioxide, and the metallic residue is weighed. Whenever the hydrated oxides of the platinum metals are ignited, either in hydrogen or in air, they have a tendency to deflagrate, which has been attributed to the splitting off of the water of hydration. This tendency to deflagrate is practically eliminated by impregnating the filter and precipitate with ammonium chloride or sulfate before igniting.

The hydrated oxide of ruthenium is ignited in air to anhydrous oxide, and then reduced in hydrogen to metal. The hydrated oxides of iridium and rhodium are treated similarly. However, when rhodium has been separated from iridium by titanous chloride, it is preferable to recover it as sulfide. In this instance the solution of rhodium sulfate must first be converted to one of rhodium chloride, by treating the strong sulfuric acid solution containing the rhodium with strong hydrochloric acid. Rhodium is precipitated easily and completely by hydrogen sulfide from a solution of its chloride, but it is only partially or not at all precipitated from its sulfate. The sulfide of rhodium is ignited in air to an anhydrous oxide, which is in turn reduced to metal in hydrogen.

Platinum is also recovered as sulfide, ignition of which in air yields spongy metal. Unlike rhodium, platinum retains a small but significant amount of sulfur which must be eliminated if high accuracy is desired. The elimination of sulfur is best accomplished by dissolving the spongy platinum and reprecipitating it by reduction with a reagent such as formic acid. It is necessary to adjust the acidity of the solution to a certain range in order to obtain complete precipitation. Whereas formerly it was recommended to use sodium acetate for this purpose, it was found that it is simpler and preferable merely to add sodium hydroxide until the acidity is reduced to that corresponding to the end point of brom phenol blue (pH 4). If the acidity is maintained at this concentration, reduction to metal is complete, the necessity of boiling is eliminated, and the operation can be conducted at the temperature of the steam bath. Furthermore, the reduction can be accomplished in solutions containing appreciable amounts of sodium salts, a condition which is unfavorable to the use of sodium acetate. Thus, the necessity of making a preliminary precipitation with hydrogen sulfide may often be avoided.

Palladium sulfide cannot be ignited to metal. Often the precipitate will fuse to a globule which strong ignition neither in air nor in hydrogen is able to decompose. Palladium, therefore, should never be determined by igniting its sulfide. It is best determined either by weighing its glyoxime compound or by igniting this compound to metal. The residue obtained is an oxide of uncertain composition which can be converted to metal by ignition in carbon dioxide. Common practice has been to reduce the oxide in hydrogen. When this is done, it is necessary to heat the metal briefly in carbon dioxide, to eliminate the hydrogen which it adsorbs. Since the oxide can be decomposed by ignition in carbon dioxide, it is simpler to dispense with the treatment with hydrogen.

E. PROCEDURE FOR THE SYSTEMATIC SEPARATION AND DETERMINATION OF THE PLATINUM METALS

Detailed directions for the systematic separation of the platinum metals from one another and for their recovery and determination are given in the publication by Gilchrist and Wichers (759). As this publication is easily accessible, no description of the procedure is given here.

F. SEPARATION OF THE PLATINUM METALS FROM OTHER ELEMENTS

In the analysis of commercial platiniferous material it becomes necessary to separate the platinum metals from whatever other elements the material contains.

The most complex naturally occurring platiniferous material is native grain platinum. That which is being recovered in Alaska contains, as major constituents, platinum, iridium, iron, gold, osmium; as minor constituents, rhodium, ruthenium, copper, palladium, silver; as small but chemically determinable constituents, chromium, nickel; and in addition, as constituents detected spectrochemically but not analytically, manganese, cobalt, aluminum, titanium, tin, lead, arsenic, silicon, antimony, magnesium, calcium, strontium, and barium.

The quantity of magnesia and silica may vary considerably, depending upon the degree to which the native platinum is cleaned mechanically.

The modern dental gold alloys represent a general type of material which is frequently encountered in platinum analysis. These alloys always contain silver, gold, and copper; they frequently contain palladium, platinum, tin, and zinc; and occasionally they contain iridium, rhodium, nickel, and indium.

The above-named base metals are the ones which are of chief interest to the analyst.

Osmium and ruthenium are usually isolated in the early stages of an analysis, by distilling their respective tetroxides. This early removal is necessary to avoid their loss by reaction with reagents which must be used. In the discussions which follow it is understood that osmium and ruthenium are absent or have been removed in the manner indicated.

1. Separation by means of hydrogen sulfide

Palladium, rhodium, and platinum form insoluble sulfides in hot acid solutions of their chloro compounds, and thus, by precipitation with hydrogen sulfide, these metals can be separated from those elements which do not form insoluble sulfides. Iridium also forms a sulfide, but complete precipitation of it is difficult to attain. Precipitation with hydrogen sulfide does not separate the four named platinum metals from other elements which form insoluble sulfides in acid solution. The utilization of sulfide precipitation, therefore, is limited and applicable only to certain combinations of elements.

2. Separation by means of reduction to metal

Palladium, rhodium, and platinum are precipitated as finely divided metals by the reducing action of various reagents, such as formic acid, hydrazine, zinc, magnesium, etc. The complete reduction of compounds of iridium is difficult to accomplish. In certain instances separations based on reduction to metal can be effected. As a means of general separation, however, reduction to metal is not recommended.

3. Utilization of hydrolytic reactions in the separation of the platinum metals from other elements

The best general method for the separation of the platinum metals from the base metals with which they are usually associated is the hydrolytic precipitation of the base metals in a solution which is treated with sodium nitrite. If a solution which contains platinum, rhodium, and iridium, in the form of their chloro compounds, is treated with sodium nitrite and heated, the chloro compounds are converted to nitrito compounds. The complex compounds formed are $Na_2[Pt(NO_2)_6]$, $Na_3[Rh(NO_2)_6]$, and $Na_3[Ir(NO_2)_6]$. Each of these three compounds is quite stable and is not decomposed in boiling solutions the alkalinities of which are between pH 12 and pH 14. The palladium complex, $Na_2[Pd(NO_2)_4]$, is stable at pH 8, but it begins to decompose, probably because of hydrolysis, with

the deposition of a brown precipitate, at an alkalinity approaching pH 10, and it is probably all decomposed at a slightly higher alkalinity.

Many of the non-platinic elements form insoluble hydroxides or hydrated oxides when the concentration of hydrogen ion in solution is adjusted to within the range pH 1 to 10, and particularly within the range pH 8 to 10. It is thus possible to remove collectively a considerable number of base metals.

(a) Hydrolytic behavior of individual elements in solutions containing sodium nitrite

The following elements are quantitatively precipitated as hydrated oxides in boiling solutions containing sodium nitrite, at the end point of thymol blue (approximately pH 10): copper, zinc, indium, titanium, zirconium, hafnium, thorium, chromium, manganese, iron, cobalt, and nickel.

Bismuth and cadmium appear to be completely precipitated at the end point of xylenol blue (approximately pH 8), if carbonate is present.

Gold is precipitated as metal by the reducing action of nitrite. Complete precipitation of it is attained when the acid solution is neutralized to pH 6.

Precipitation of aluminum hydroxide is complete at the end point of brom cresol purple (approximately pH 6.3). At increasing alkalinities aluminum hydroxide becomes more and more soluble.

Precipitation of gallium hydroxide is complete at the end point of brom phenol blue (pH 4) and at the end point of chlor phenol red (pH 6). It is entirely redissolved at the end point of xylenol blue.

Uranium, if taken as uranyl nitrate, appears to be completely precipitated at the end point of xylenol blue.

The elements which are not precipitated in nitrite solution within the range pH 1 to 10 are the following: silver, if taken as nitrate; mercury; univalent thallium, germanium; and phosphate, arsenate, vanadate, selenate, tellurate, molybdate, tungstate, and rhenate, as sodium salts.

The acidic radicals do form precipitates with a number of metallic cations, and such compounds as lead phosphate, lead arsenate, lead vanadate, etc., deposit in the nitrite solution.

There is no alkalinity at which the hydroxide of bivalent lead is completely insoluble. Precipitation of lead as carbonate is essentially complete at pH 8; that of lead as phosphate is quantitative in the range pH 4 to 10; and that also of lead as chromate, at pH 6.3.

The hydrated oxide of tin becomes colloidal at alkalinities greater than pH 7. It is completely precipitated in filterable form in the range pH 1 to 6. In the case of tin, precipitation is best accomplished at pH 1.5 from a solution to which nitrite has not yet been added.

A method for the analysis of dental gold alloys, based on the use of nitrite, was published by Gilchrist (760), and a similar one for the analysis of alloys used in jewelry was described by Holzer and Zaussinger (393).

(b) Hydrolytic behavior of individual elements in solutions containing sodium bromate

A number of the elements react in a different manner if the solution contains sodium bromate, instead of sodium nitrite. Sodium bromate is an oxidizing reagent, and by means of it separations can be effected within the groups of elements the separation of which is accomplished through the use of nitrite.

As has been previously discussed, the quantitative separation of palladium, rhodium, and iridium from platinum is effected in a boiling solution containing bromate, when the alkalinity is within the range pH 6.3 to 8.

Gold, which is completely precipitated in nitrite solution, remains soluble in one containing bromate.

Chromium, which is precipitated as tervalent hydroxide in nitrite solution, is oxidized to the chromate state in slightly acid solutions which contain sodium bromate. This difference in behavior in the two media enables the analyst to make good use of chromium, particularly in the separation of lead from the platinum metals.

When the alkalinity of a solution which contains lead and bromate exceeds pH 7, the lead is quantitatively precipitated as hydrated lead dioxide, a reaction which is of value to the analyst.

The non-platinic elements mentioned in connection with precipitation in nitrite solution, other than those few which have just been discussed, behave in bromate solution as they do in nitrite solution, with the exception of cobalt, nickel, etc., which form products of a higher state of oxidation.

(c) Possibilities for separations under conditions of controlled alkalinity

The control of the alkalinity of a solution enables one to effect separations not only of many of the base metals from the platinum metals but, in certain instances, of base metals from one another. The extent to which controlled hydrolytic reactions, and also precipitation of definite compounds, are of value does not appear to have been fully appreciated in general analytical chemical work. A number of the possibilities for separation are here indicated. Others can be inferred from the behavior of related elements.

(1) Palladium, rhodium, iridium, and platinum can be separated from those elements which form insoluble hydrated oxides in solutions containing sodium nitrite.

(2) Chromium can be separated from those elements which form insoluble hydrated oxides in solutions containing sodium bromate.

(3) Lead can be separated from palladium, rhodium, iridium, and platinum, by precipitation as lead chromate, in solutions containing sodium nitrite.

(4) Lead can be separated, by means of sodium bromate, from those elements which form oxy acids.

(5) Copper can be separated from arsenic, selenium, and tellurium in solutions containing either sodium nitrite or sodium bromate.

(6) Arsenic can be separated from palladium, rhodium, and iridium in solutions containing sodium bromate.

(7) Vanadium can be separated from aluminum, titanium, manganese, iron, cobalt, nickel, palladium, rhodium, and iridium in solutions containing sodium bromate.

(8) Mercury can be separated from copper and zinc in solutions containing sodium nitrite.

(9) Germanium can be separated from gallium and indium, and gallium can be separated from indium, merely by adjusting the alkalinity of the solution, without the aid of nitrite or bromate.

(10) Osmium and ruthenium can be separated, by hydrolytic precipitation of their hydrated oxides, from rhenium, which does not precipitate.

4. Utilization of fire-assay methods

The methods commonly used for the rapid evaluation of platiniferous materials have been those of fire assay. The value of fire-assay methods consists in the separation and collection of the platinum metals, the amount of which may be exceedingly small, from a large quantity of extraneous matter. In this respect these methods accomplish quickly what would otherwise be a tedious task. The difficulty with assay methods has been, however, that ultimately the separation of the platinum metals from one another must be effected by wet methods.

In 1936 Beamish and his associates in Canada attacked the problem of placing fire-assay methods for the platinum metals on a firm foundation. Their publications (636 to 644) constitute an outstanding contribution to this phase of analytical determination. In their work these investigators utilized hydrolytic methods of separation and thus combined the desirable features of fire-assay methods with those of the latest wet methods.

VII. Atomic Weights of the Platinum Metals

Determination of the chemical atomic weights (783) of the platinum metals has rested almost exclusively on the preparation and analysis of complex compounds, for the most part the potassium and ammonium salts of the chloro and bromo acids. In addition, the ammines have been utilized in the cases of rhodium, palladium, and ruthenium. In only one instance has a determination been made by ascertaining the metallic content of an oxide, namely, that of ruthenium dioxide, RuO_2.

In the years just preceding the outbreak of the World War of 1914, the chief center of activity on the atomic weights of the platinum metals was Gutbier's laboratory at the University of Erlangen.

A. DETERMINATION OF ATOMIC WEIGHTS BEFORE 1915

With the exception of two published accounts (337, 751), all of the work on the chemical atomic weights of the platinum metals was done prior to 1915. A brief review of it is here given.

1. Ruthenium

The atomic weight of ruthenium was determined first by Claus, the discoverer of ruthenium, who prepared K_2RuCl_5, the true composition of which was not

clarified until about fifteen years ago. Later than Claus, Joly determined the ruthenium content of RuO_2, of $RuCl_3NO \cdot H_2O$, and of $(NH_4)_2[RuCl_5NO]$. In 1912 Vogt redetermined the ruthenium content of RuO_2.

2. Rhodium

The first determination of the atomic weight of rhodium was made by Berzelius, who prepared $Na_3[RhCl_6]$ and K_2RhCl_5. He calculated the atomic weight from the percentages of rhodium, chlorine, and of sodium chloride and potassium chloride, and likewise obtained ratios between the rhodium and chlorine, sodium chloride, and potassium chloride. Berzelius' methods became the standard pattern for all subsequent work of this type.

Jörgensen determined rhodium in chloropentamminerhodium chloride, $[Rh(NH_3)_5Cl]Cl_2$, and Seubert and Kobbe repeated the work, as did also Hüttlinger, and Dittmar. Renz determined rhodium in $[Rh(NH_3)_5Br]Br_2$.

3. Palladium

Berzelius' first attempt to obtain the atomic weight of palladium was with palladium sulfide. Later, he analyzed $K_2[PdCl_4]$ for Pd, 2KCl, and Cl_2. Keiser determined the palladium content of $[Pd(NH_3)_2Cl_2]$. This determination was subsequently repeated by Bailey and Lamb, and by Keller and Smith. Joly and Leidié, in their work, returned to the compound $K_2[PdCl_4]$.

Hardin obtained the metal content of $[Pd(C_6H_5NH_2)_2Cl_2]$, $[Pd(C_6H_5NH_2)_2-Br_2]$, and $(NH_4)_2[PdBr_4]$.

Amberg utilized $[Pd(NH_3)_2Cl_2]$ and determined the ratio $2AgCl:[Pd(NH_3)_2-Cl_2]$, as well as the palladium content. Krell, and also Woernle, determined the quantity of metal in $[Pd(NH_3)_2Cl_2]$, while Haas did the same with $[Pd(NH_3)_2-Br_2]$, as also did Gebhardt. Kemmerer repeated the determination of palladium in $[Pd(NH_3)_2Cl_2]$ and, in addition, obtained that in $[Pd(NH_3)_2(CN)_2]$. The last work on $[Pd(NH_3)_2Cl_2]$ was done by Shinn.

4. Osmium

The atomic weight of osmium was determined by Berzelius, by Fremy, by Seubert, and by Seybold. Berzelius determined the amount of osmium and of potassium chloride in $K_2[OsCl_6]$. Fremy's results were based on the composition of OsO_4. The work upon which the atomic weight of osmium rested for many years was that of Seubert, who prepared and analyzed $K_2[OsCl_6]$ and $(NH_4)_2[OsCl_6]$. In 1912 Seybold reported the osmium content of $(NH_4)_2[OsCl_6]$.

5. Iridium

As usual, the earliest determination of the atomic weight of iridium was made by Berzelius, who analyzed $K_2[IrCl_6]$. This was followed by that of Seubert, who, in addition, analyzed $(NH_4)_2[IrCl_6]$. Joly determined the amount of iridium and of potassium chloride in $K_3[IrCl_6] \cdot 3H_2O$, and of iridium in $(NH_4)_2[IrCl_6]$. Hoyermann, and also Holzmann, repeated the work of Seubert on the determination of the iridium content of $(NH_4)_2[IrCl_6]$. Archibald, in 1909, published a preliminary note on the analysis of $K_2[IrCl_6]$.

6. Platinum

Berzelius determined the metal content of platinous chloride, and later studied $K_2[PtCl_6]$, which compound was also analyzed by Andrews. Seubert analyzed $(NH_4)_2[PtCl_6]$ and $K_2[PtCl_6]$. Halberstadt also utilized these compounds and, in addition, the corresponding bromo salts, as well as $PtBr_4$. This work was followed by that of Dittmar and McArthur on $K_2[PtCl_6]$.

The most thoroughly conducted and reliable work on the atomic weight of platinum was that of Archibald in 1909.

B. DETERMINATION OF ATOMIC WEIGHTS SINCE 1915

Very little interest has been taken in the determination of the atomic weights of the platinum metals by the usual chemical methods during the past quarter of a century. Only two pieces of work were published, that of Gilchrist (751) on osmium, and that of Gleu and Rehm (337) on ruthenium.

The chief interest during this period has been that of physicists, who, from a knowledge of the number, mass, and proportion (809) of the isotopes, have calculated values which, in the cases of platinum and rhodium, agree with those determined chemically. The recently determined chemical value of Gleu and Rehm for ruthenium is in agreement with that determined earlier by Aston.

Sampson and Bleakney (808) reported the value for palladium as 106.6; for iridium, as 192.2; for rhodium, as 102.89; and for platinum, as 195.23. The chemically determined values are 106.7, 193.1, 102.91, and 195.23, respectively.

Nier (804) redetermined the isotopic abundance ratios of osmium, using osmium tetroxide. These led to an atomic weight of 190.21 (packing fraction, -1×10^{-4}; conversion factor, 1.00027), which is considerably lower than that found by Gilchrist (751), 191.5, the accepted value from 1935 to 1938, from the osmium content of $(NH_4)_2[OsCl_6]$ and of $(NH_4)_2[OsBr_6]$.

Gleu and Rehm (337) reported the atomic weight of ruthenium as 101.1, from the ruthenium content of $[Ru(NH_3)_5Cl]Cl_2$.

In this connection, it is interesting to note that the atomic weight of gold, a metal closely related to platinum, as determined by physical means (781) has a value of 196.99. The long-accepted chemical value is 197.2.

The discrepancies which exist between the chemically determined atomic weights of osmium and of iridium and those calculated from estimates of isotopic ratios need to be cleared up. Unfortunately, there are few possibilities for obtaining the chemical atomic weights of the platinum metals by determining the metallic content of their oxides. In the case of osmium, its tetroxide might be considered, as Fremy tried to do years ago. Here, however, one is handicapped by the small ratio involved and by the difficulties which arise in handling such an unstable compound.

VIII. CONSTITUTION OF COMPOUNDS OF THE PLATINUM METALS

To gain any sort of an understanding of the chemistry of the platinum metals, it is necessary to think in terms of coördination compounds. There appears to be no other way by which to grasp easily a clear idea of the complicated reactions

encountered. In that which is presented here, no attempt has been made to include intricate details of conditions under which various reactions and transformations are conducted. Such matters are fully described in publications by the original authors. Rather, the purpose has been to assemble certain ideas and features concerning the complex nature of the compounds of the platinum metals for the benefit of those not particularly conversant with the subject of coördination compounds.

A. THE THEORY OF WERNER

When used in a chemical sense, the term "coördination" is applied to a mode of atomic linking first recognized by Alfred Werner (778). His theory, which he first suggested in 1891 and developed more fully in 1893, originated in an attempt to explain the structure of a series of so-called molecular or complex compounds formed by the combination of apparently saturated molecules, and especially the compounds which many salts form with ammonia. The hypotheses proposed by him in explanation of the results of his researches are embodied in the coördination theory, which affords a simple and comprehensive explanation of the chemical constitution of the most diverse types of metallic salts. In the chemistry of the metallic elements, and especially so in the case of the platinum metals, few generalizations have proved so fruitful as those based on the study of molecular compounds, that is, of those compounds formed by the union in stoichiometric ratio of otherwise saturated molecules themselves capable of independent existence. The coördination theory of Werner has proved far-reaching in its scope, and has been fully substantiated by both chemical and physical evidence.

According to Werner, without invoking any special theory of valency, neutral molecules or negatively charged ions are grouped or coördinated around a central atom in the "first sphere of attraction", or coördination sphere. The number of groups which may be so arranged about the central atom is the coördination number, and is a characteristic property of that atom. In general, the coördination number can assume only those values (2, 3, 4, 6, 8) which allow of spatially symmetrical arrangements, the values 6 and 4 being the most usual. Werner assigned definite positions in space to the groups in a coördination complex. Where these were 4, an arrangement at the points of a tetrahedron had already been established for carbon by van't Hoff, but Werner showed that a different arrangement must occur in the 4-coördinate compounds of platinum. These compounds of platinum are never optically active. Compounds of the type PtA_2B_2 occur in two geometrically isomeric forms, which is possible if the four groups are in the same plane with the central atom, but not if they occupy the corners of a tetrahedron. To the groups in a 6-coördinate complex, Werner assigned the simplest distribution in three dimensions, at the points of an octahedron, and justified this by showing that certain compounds, which on this assumption must have asymmetric molecules, could be resolved into optically active forms.

The compound $[Pt(NH_3)_6]Cl_4$ is capable of ionizing into the complex ion

$[Pt(NH_3)_6]^{4+}$, with a net positive charge of four units, and four Cl^- ions. In such a compound Werner regarded the chlorine as bound in the "second sphere of attraction".

1. Ammines of the platinum metals

All the metals of the platinum group form ammines, that is, compounds in which ammonia is bound to the metallic atom. The following compounds of quadrivalent platinum and of bivalent platinum will serve as illustrations:

Derivatives of quadrivalent (6-coördinate) platinum

Hexammineplatinic chloride............	$[Pt(NH_3)_6]Cl_4$
Chloropentammineplatinic chloride	$[Pt(NH_3)_5Cl]Cl_3$
Dichlorotetrammineplatinic chloride....	$[Pt(NH_3)_4Cl_2]Cl_2$
Trichlorotriammineplatinic chloride.....	$[Pt(NH_3)_3Cl_3]Cl$
Tetrachlorodiammineplatinum (*cis*- and *trans*-isomers)....	$[Pt(NH_3)_2Cl_4]$
Potassium pentachloroammineplatinate.	$[Pt(NH_3)Cl_5]K$
Potassium hexachloroplatinate....	$[PtCl_6]K_2$

Derivatives of bivalent (4-coördinate) platinum

Tetrammineplatinous chloride..........	$[Pt(NH_3)_4]Cl_2$
Chlorotriammineplatinous chloride......	$[Pt(NH_3)_3Cl]Cl$
Dichlorodiammineplatinum (*cis*- and *trans*-isomers).....	$[Pt(NH_3)_2Cl_2]$
Potassium trichloroammineplatinite..	$[Pt(NH_3)Cl_3]K$
Potassium tetrachloroplatinite......	$[PtCl_4]K_2$

The value of the molecular conductivity at 25°C. at infinite dilution is found to be 523 for hexammineplatinic chloride, which indicates dissociation of the compound into five ions. With succeeding substitution the conductivity falls to values consistent with four ions, three ions, two ions, and no ions. Zero conductivity corresponds to the compound $[Pt(NH_3)_2Cl_4]$, which consists only of the nullvalent coördinate complex. The further entrance of a chloride ion into the complex results in a net charge on it of one negative unit, and the dissociation of the compound into two ions. The end member of the series is the familiar $K_2[PtCl_6]$, which dissociates into three ions with a conductivity of 256. As will be seen later, the nullvalent compounds have a special interest.

2. Nomenclature of coördinate compounds

The nomenclature devised by Werner still regulates the naming of coördination compounds and its value lies in the fact that it permits uniform treatment

of the whole range of compounds. An alteration is needed only as regards the indication of valency.

In the case of complex cations, the constituents of the complex are taken first, and the atoms or groups coördinated are mentioned in the order (*1*) *acidic groups*, such as chloro (Cl), cyano (CN), cyanato (NCO), thiocyanato (NCS), sulfato (SO₄), sulfito (SO₃), carbonato (CO₃), nitro (NO₂), nitrito (ONO), oxalato (C₂O₄), and hydroxo (OH); (*2*) *neutral groups*, such as aquo (H₂O), pyridino (C₅H₅N), and substituted amines (C₂H₄(NH₂)₂); and (*3*) last of all, preceding the metal itself, ammine (NH₃).

The names of the constituents of the complex are written as one word. It is to be noted that the ammonia molecule is designated as "ammine" and spelled with a double "m" to distinguish the word from "amine", which refers to a substituted ammonia. The Greek prefixes di, tri, tetra, penta, hexa, etc., are used to indicate the number of each coördinated group, the prefix mono being self-evident and unnecessary. For example, [Pt(NH₃)₃py₂Cl]Cl₃ would be named chlorodipyridinotriammineplatinic chloride. If the central atom is in the anionic complex, as it is in K[Pt(NH₃)Cl₅] and K₂[PtCl₆], the compounds are named potassium pentachloroammineplatinate and potassium hexachloroplatinate, respectively, the names of the constituents of the complex again being written as one word. In the case of nullvalent complexes, such as [Pt(NH₃)₂Cl₄] and [Pt(NH₃)₂Cl₂], the names are written tetrachlorodiammineplatinum and dichlorodiammineplatinum, again as one word.

While the above system of nomenclature serves admirably well, a more precise designation of the valency of the central atom is needed, and the Committee of the International Union of Chemistry for the Reform of Inorganic Chemical Nomenclature has so recommended (797). Instead of designating the valency of the central atom by -ous and -ic, the Committee has proposed the use of Roman figures expressing the valency to be placed in parentheses after the names of the elements to which they refer. [Pt(NH₃)₅Cl]Cl₃ would thus be named chloropentammineplatinum(IV) chloride, and [Pt(NH₃)₃Cl]Cl, chlorotriammineplatinum(II) chloride. In the case of complex anions of acids or salts, the valency of the central atom is given in parentheses after the name of the complex which ends in -ate. The Latin names of metals must often be used in this connection for reasons of euphony. K₂[PtCl₆] would be called potassium hexachloroplatinate(IV), and K₂[PtCl₄], potassium tetrachloroplatinate(II). By these rules, potassium ferrocyanide, K₄[Fe(CN)₆], and potassium ferricyanide, K₃[Fe(CN)₆], become potassium hexacyanoferrate(II) and potassium hexacyanoferrate(III), respectively. Potassium cobaltinitrite, K₃[Co(NO₂)₆], becomes potassium hexanitritocobaltate(III). Mention of the valency of the central atom is not necessary when the number of ionized atoms or groups is given in the name as, for example, [Pt(NH₃)₆]Cl₄, hexammineplatinum tetrachloride; K₄[Fe(CN)₆], tetrapotassium hexacyanoferrate; K₃[Fe(CN)₆], tripotassium hexacyanoferrate. This last-named method of naming is to be recommended only in those cases where the electrochemical valency of the

central atom is not known or is not known with certainty as, for instance, with compounds containing NO in the complex, such as $K_2[RuCl_5NO]$. In the case of the nullvalent complexes $[Pt(NH_3)_2Cl_4]$ and $[Pt(NH_3)_2Cl_2]$, it is not necessary to give the valency of the central atom.

3. Groups which behave like ammonia in the coördination sphere

Although ammonia was the first of the neutral nitrogen compounds to be introduced into the coördination complex, it is not the only one in which the coördinating ability of nitrogen has been utilized. Certain other compounds of nitrogen have even more interest for the chemist than has ammonia. Besides nitrogen compounds, those containing sulfur, selenium, phosphorus, and arsenic have been used as neutral coördinating groups. The following list will give the reader an idea of the types of compounds which have been used in preparing coördination compounds of the platinum metals.

(a) Organic compounds containing nitrogen

Amines: Methyl-, ethyl-, propyl-, butyl-, and amyl-amines; benzylamine, phenylamine (aniline), toluidine, xylidine, p-phenetidine; diethyl- and dipropyl-allylamines; 1,2,3-triaminopropane; ethylenediamine, propylenediamine.

Amidines: Guanidine.

Amino acids: Glycine.

Nitriles: Propionitrile, benzonitrile; 1,2-dicyanobenzene, 1,2-dicyanonaphthalene.

Isonitriles: Methyl-, butyl-, and phenyl-carbylamines.

Dioximes: Dimethylglyoxime.

Compounds containing nitrogen in the ring: Pyridine, picoline, lutidine, collidine, piperidine; quinoline; pyrazole, glyoxaline; 2,2'-dipyridyl; 2,2'2''-tripyridyl, o-phenanthroline; pilocarpine, nicotine, strychnine, brucine.

(b) Organic compounds containing sulfur

Methyl, ethyl, propyl, butyl, and benzyl sulfides; diethylene disulfide; dimethyl-, diethyl-, dipropyl-, and dibutyl-dithioethyleneglycols; diethyl- and dipropyl-dithiotrimethyleneglycols; thiocarbamide (thiourea), methyl-, ethyl-, and undecyl-thiocarbamides; diethyl- and triethyl-thiocarbamides; thioacetamide; xanthogenamide.

(c) Organic compounds containing selenium, tellurium, arsenic, and phosphorus

Ethyl selenide; diethyldiselenotrimethyleneglycol; triethylarsine; trimethylphosphine and triethylphosphine.

4. Abbreviations commonly used

To save time and confusion in writing formulas, it has been necessary to make use of abbreviations, or more properly symbols, to indicate many of the co-

ordinating groups. The more familiar ones encountered in the literature are listed below:

SYMBOL	COÖRDINATING GROUP		SYMBOL	COÖRDINATING GROUP
ac	Acetylacetone		py.... .	Pyridine
ec	Ethylenediaminebisacetylacetone		qu... .	Quinoline
en .. .	Ethylenediamine		pic.... . .	Picoline
et.	Ethylene		tu . . .	Thiourea
etn. . .	Ethylamine		tpn...	1,2,3-Triaminopropane
etu. . . .	Ethylenethiourea		tren .	Tri-(β-aminoethyl)amine
hx	Hydroxylamine		phenan .	o-Phenanthroline
ox	Oxalate radical		dipy..... .	Dipyridyl
mn	Methylamine	.	tripy.. .	Tripyridyl

B. MANIFOLD ASSOCIATING GROUPS

Among the various associating groups which have been mentioned there are some which differ from ammonia in having the ability to fill more than one position in the coördination complex, and it is this property that makes them of interest and use in the study of structure.

1. Unidentate (unifunctional) groups

In $[Pt(NH_3)_6]Cl_4$ the ammonia molecule and in $[PtCl_6]K_2$ the chloride ion each occupy only one position within the coördination sphere, and a similar degree of association is manifested by water, the hydroxo group, oxygen, pyridine, methylamine, dialkyl or diaryl sulfide, phosphine, arsine, and many other molecular species.

2. Bidentate (bifunctional) groups

Compounds such as ethylenediamine, $NH_2CH_2CH_2NH_2$, and radicals such as the oxalato group, C_2O_4, each of which functions in the coördination sphere as two associating units or doubly bound groups, often to form exceedingly stable coördination compounds, have been classed by Sir Gilbert Morgan (802) under the convenient general term of chelate groups, after the Greek noun, singular, ἡ χηλή, a cloven hoof, as of an ox; plural, αἱ χηλαί, as of a crab's claws. Certain of these chelate groups have played an important part in the demonstration of the stereochemical structure of coördination compounds. 2,2'-Dipyridyl,
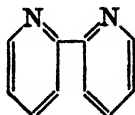
and o-phenanthroline,
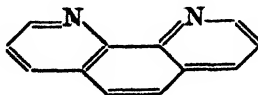
furnish examples of such chelate groups, both of which were employed by Werner in the demonstration of octahedral structure. The orange-red bivalent ruthenium salt [Rudipy₃]Cl₂·6H₂O was found by Burstall (542) to be sufficiently stable for resolution into optically active forms.

Chelate groups need not be organic, as was demonstrated by Werner in the case of hexoldodecamminetetracobaltic chloride, and by Mann in the case of the sulfamide compound of rhodium, both of which are discussed later under the heading of inorganic optical activity.

3. Tridentate and quadridentate groups

In addition to the numerous bifunctional chelating groups there are a few compounds known which are capable of filling three (tridentate or trifunctional groups) or even four (quadridentate or quadrifunctional groups) positions in the coördination sphere.

As typical tridentate groups there may be cited tripyridyl and 1,2,3-triaminopropane. These form very stable compounds with the 6-coördinate metals, of the types [Mtripy₂]X₂ and [Rhtpn₂]I₃ (543). In such compounds the coördinated group is probably attached in the 1,2,6-positions along the octahedron edge, as shown by the fact that the same tridentate groups readily fill three coördination positions in the planar 4-coördinate complex, as in [Pt tripy-Cl]Cl. It can be shown that such a structure is strainless only if the platinum atom and the whole tripyridyl molecule are coplanar.

A fourfold associating unit is furnished by the bivalent radical of ethylenediaminebis(acetylacetone), {CH₂N:C(CH₃)CH:C(OH)CH₃}₂, which forms a remarkably stable complex with palladium. Tri(β-aminoethyl)amine, N(CH₂-CH₂NH₂)₃, also behaves as a fourfold associating compound and gives rise to the platinum salts [Pttren]I₂ and [PtCl₂tren]Cl₂.

The subject of quadridentate groups should not be dismissed without mention of the particularly important metallic derivatives of the porphyrin skeleton. These compounds are deeply involved in the vital processes of both the vegetable and the animal kingdoms. Chlorophyll, and the hemin of blood, contain the magnesium and iron inner complex salts of porphyrin derivatives. A similar type of derivatives is known as the phthalocyanines, a series of metallic complexes of great stability conveniently produced by heating a metal or its chloride with 1,2-dicyanobenzene. In the phthalocyanine, as in the porphyrin, the coördinating group forms a rigid planar structure of just such dimensions as to accommodate a metal ion.

4. Ring size and chelation

For a molecule with two potentially coördinating groups, such as a diamine, NH₂(CH₂)ₙNH₂, or an amino acid, NH₂(CH₂)ₙCOOH, to function as a chelate group, it must be geometrically possible to form a ring of low strain, precisely as in the formation of carbon rings in organic chemistry. Chelation will therefore be most favored when the groups are in the 1,4- or the 1,5-positions.

Where saturated (single-linked) rings are formed, as by the coördination of diamines, the five-membered ring,

$$
\begin{array}{c}
\text{NH}_2\text{—CH}_2 \\
\nearrow \\
\text{Pt} \\
\nwarrow \\
\text{NH}_2\text{—CH}_2
\end{array}
$$
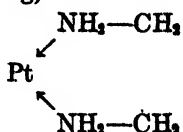
as formed by ethylenediamine, is the most stable. Objective proof of this was furnished by Drew (574), who found that ethylenediamine and, less readily, 1,3-propylenediamine coördinate with platinum, whereas the higher poly-methylenediamines form only amorphous ill-defined products, in which the two amino groups of any one molecule of diamine are probably linked to different metallic atoms.

A demonstration of the superior stability of the five-membered, as compared with the six-membered, ring was given by Mann (546) in studying the coördination compounds of 1,2,3-triaminopropane, $NH_2CH_2CH(NH_2)CH_2NH_2$. This compound *can* react so as to occupy *only two* coördination positions, the third amino group then being capable of salt formation. The compound of this type formed with platinic chloride will then be asymmetric,

$$
\begin{array}{c}
\text{NH}_2\text{—CH}_2 \\
\nearrow \\
\text{Cl}_4\text{Pt} \\
\nwarrow \\
\text{NH}_2\text{—CH} \\
| \\
\text{CH}_2\text{—NH}_2\cdot\text{HX}
\end{array}
$$

or symmetrical,

$$
\begin{array}{c}
\text{NH}_2\text{—CH}_2 \\
\nearrow \qquad\qquad \searrow \\
\text{Cl}_4\text{Pt} \qquad\qquad \text{CH} \\
\nwarrow \qquad\qquad \nearrow\ | \\
\text{NH}_2\text{—CH}_2 \\
\\
\text{NH}\cdot\text{HX}
\end{array}
$$
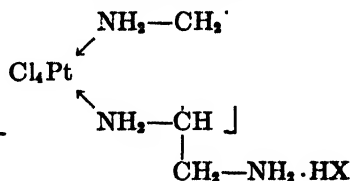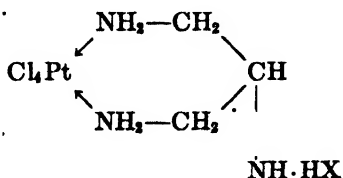
according as a five-membered ring or a six-membered ring is formed preferentially by chelation. Mann resolved the compound into optical isomers, thereby establishing the structure with a five-membered chelate ring.

Where chelate rings involving double bonds are formed, the formation of six-membered rings is favored. It is thus the β-diketones which most readily give rise to inner complex salts.

Determinations of the configuration of stereoisomeric series depend on the fact that bifunctional groups, such as ethylenediamine or the oxalato group, can, from considerations of molecular dimensions, span only *cis*, or 1,2-, positions. Hence, provided that no intramolecular change of configuration occurs during reaction, the isomer which is capable of reacting with a chelating group must belong to the *cis*-series.

C. ISOMERISM

In considering coördination compounds, it soon becomes apparent that a number of types of isomerism are possible.

1. Ionization isomerism

Examples of a type of isomerism which Werner termed ionization isomerism are the violet red $[Co(NH_3)_5Br]SO_4$ and the red $[Co(NH_3)_5SO_4]Br$; $[Co(NH_3)_5Br]$-C_2O_4 and $[Co(NH_3)_5C_2O_4]Br$; $[Pt(NH_3)_4(OH)Cl]SO_4$ and $[Pt(NH_3)_4(OH)SO_4]Cl$; $[Pt(NH_3)_4Cl_2]Br_2$ and $[Pt(NH_3)_4Br_2]Cl_2$.

It is important to note that in certain cases dibasic acid radicals may occupy only one position in the coördination complex. While occupying only one coördination position and being un-ionized, the sulfato group neutralizes two of the ionic charges on the cobalt, making the whole complex ion univalent. In the example cited, the oxalato group behaves in a similar manner.

2. Salt isomerism

A type of isomerism associated with the potential existence of isomeric forms of the acid radical bound within the complex was termed salt isomerism by Werner. This is exemplified by the unstable scarlet $[Co(NH_3)_5(ONO)](NO_3)_2$ and the stable yellow-brown $[Co(NH_3)_5NO_2](NO_3)_2$. Other examples are the unstable *cis- and trans-* $[Coen_2(ONO)_2]X$ and the corresponding nitro compounds, $[Coen_2(NO_2)_2]X$; the unstable $[Copy_2(NH_3)_2(ONO)_2]X$ and the stable $[Copy_2(NH_3)_2(NO_2)_2]X$.

Although no examples were noted in the literature, this type of isomerism presumably exists in the case of the platinum metals.

The only apparent seat of isomerism is in the $-NO_2$ group, which might, as in the organic nitrous esters and nitro compounds, react either as $-O-N=O$ or as $-N\!\!\diagup\!\!\diagdown\!\!\begin{smallmatrix}O\\O\end{smallmatrix}$.
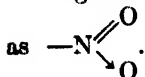
3. Stereoisomerism

In harmony with Werner's conception of the equivalence of the coördination positions, it has been seen that complex ions of the type $[MA_5B]$, where A is NH_3 and B is H_2O or Cl, exist in only one form except where salt isomerism occurs. The substitution of a second group, giving a complex of the type $[MA_4\text{-}XY]$, must lead to the possibility of stereoisomerism and the number of isomers should indicate the spatial arrangement of the groups. A regular octahedral arrangement leads to two disubstituted products, 1,2 and 1,6.

(a) *Cis–trans* isomerism

In the 6-coördinate complexes of quadrivalent platinum, and in the 4-coördinate complexes of bivalent platinum, as examples, the possibility of *cis–trans* isomerism exists. In the octahedral arrangement of the 6-coördinate complex, the two spatial groupings of the disubstituted product may be represented as follows:

Cis-form   *Trans*-form
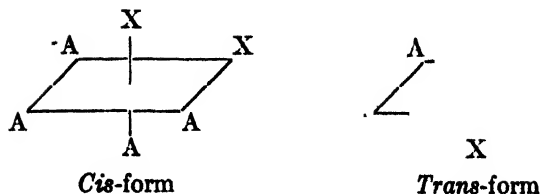
Thus, in the diacidotetrammine complex of quadrivalent platinum, $[Pt(NH_3)_4\cdot Cl_2]^{2+}$, and in the tetraacidodiammine complex, $[Pt(NH_3)_2Cl_4]$, *cis–trans* isomerism may be expected.

In the 4-coördinate complex, on the planar basis, the groupings are as follows:
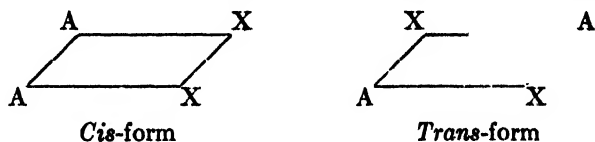
Cis-form   *Trans*-form

Examples of these arrangements are the *cis–trans* forms of dichlorodiammineplatinum, $[Pt(NH_3)_2Cl_2]$, and of dichlorodiamminepalladium, $[Pd(NH_3)_2Cl_2]$.

In the 6-coördinate triacidotriammine complexes the existence of two geometrically isomeric forms should be possible, for instance:
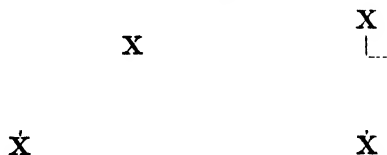
In the case of tervalent metals the complex is nullvalent.

(b) Optical isomerism

The crowning achievement of Werner's theory of coördination was the prediction of optically active compounds. In 1911 Werner accomplished the resolution of cobalt compounds with two and three chelate groups, such as $[Coen_2(NH_3)Cl]X_2$, $[Coen_2(NO_2)Cl]X$, and $[Coen_3]X_3$, into their optical antimers, and thus established his octahedral theory for cobalt. To prove that the optical activity was not caused by some rearrangement of the organic groups involved, he succeeded in 1914 in resolving the purely inorganic compound
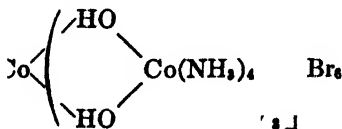
He further prepared optically active compounds containing chromium, iron, and rhodium. In 1917 Delépine (479) effected the resolution of $K_3[Ir(C_2O_4)_3]$.

The octahedral configuration of the 6-coördinate complex requires the existence

not only of geometrical isomerism of the kinds previously mentioned, but also of mirror-like isomerism, leading to optical activity.

Trans-form
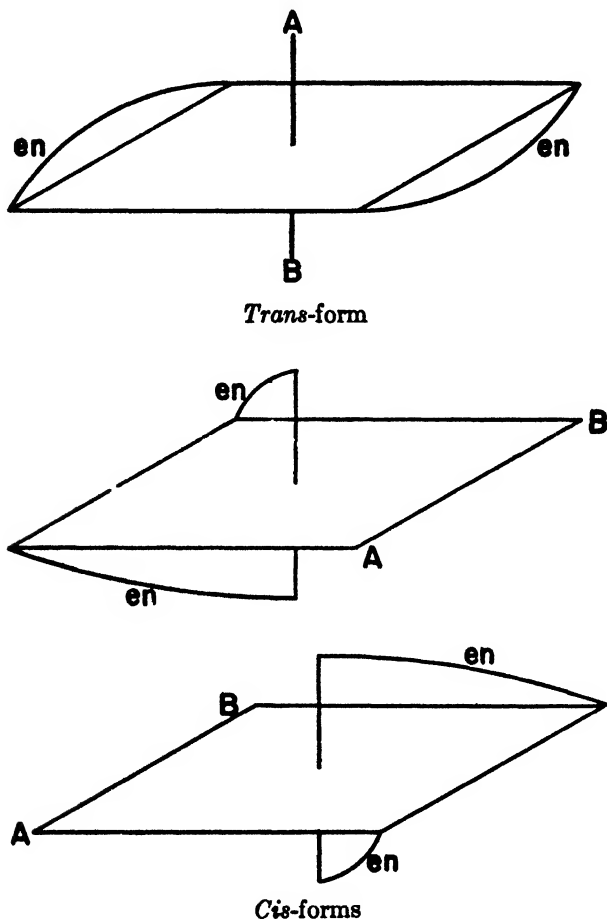
Cis-forms

The *trans*-form of the complex [Rhen$_2$AB] possesses a plane of symmetry, and so must be non-resolvable. The one *cis*-form is not superposable upon its mirror image, and the two optical isomers should be capable of resolution.

The molecular dissymmetry does not vanish if A = B. For the maintenance of dissymmetry it is not even necessary that two chelating groups should be present. *Cis*-compounds of the type [M^{III}enA$_2$B$_2$] must also display optical activity.

When three bifunctional chelating groups are introduced into the 6-coördinate complex, there is no asymmetry of any one atom but there exist only "odd" symmetry elements of the whole molecule, in the form of trigonal axes of symmetry through the centers of the octahedron faces.
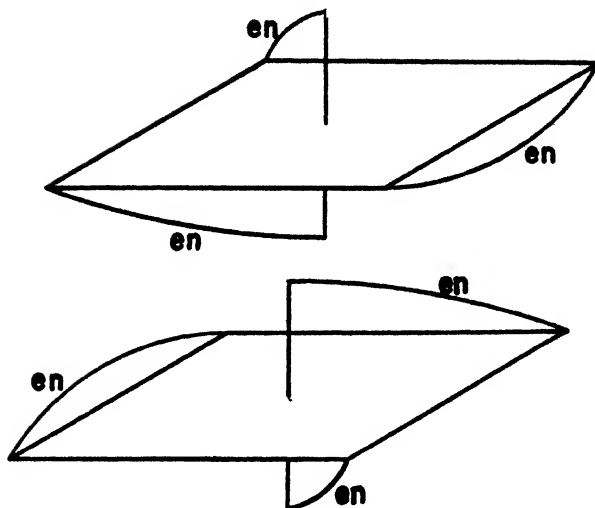
The trioxalato complexes, in which the oxalate radical acts as a chelating group, are similar in symmetry to those of the trisethylenediamino complexes.

Where an *existing* asymmetric center is introduced into a complex, the possibilities of isomerism are greatly increased, and cases arise which have no counterpart in the stereochemistry of carbon. Propylenediamine, $NH_2CH_2CH(CH_3)$-NH_2, which contains an asymmetric carbon atom, may enter into combination either in its dextro- or its levo-form. The *trans*-complex, itself not asymmetric, may then be formed either with *d*- or with *l*-pn, while two distinct series of the *cis*-isomers should exist.
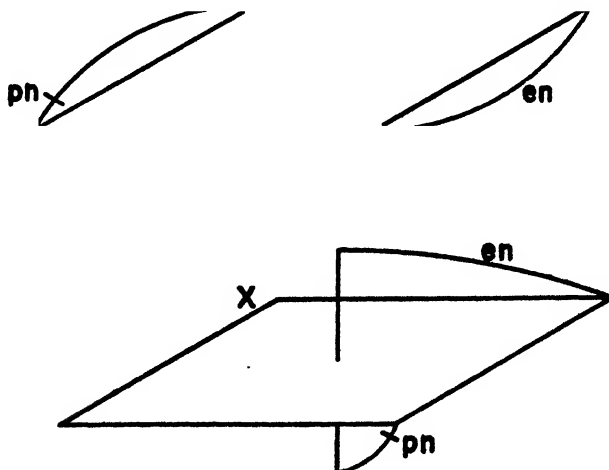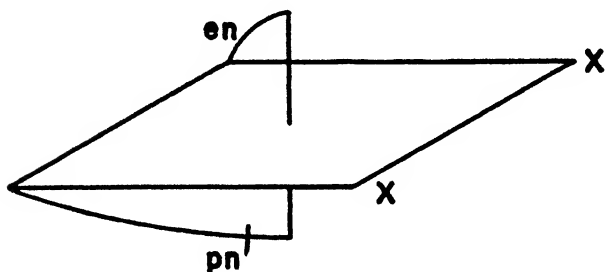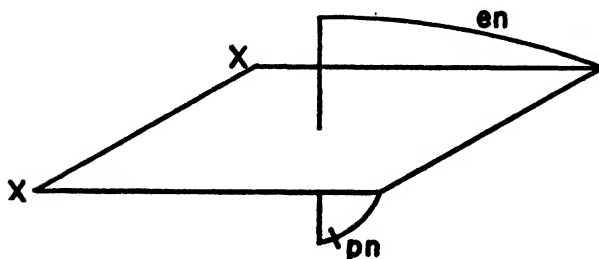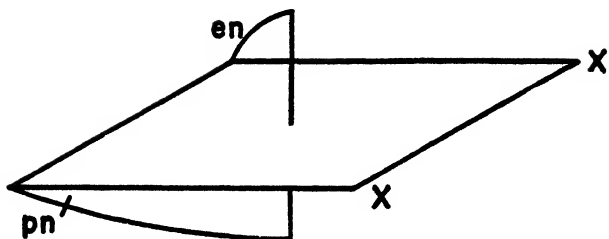
In binuclear complexes it is possible to have two asymmetric centers in the molecule. If the asymmetric centers are structurally similar, there should exist an internally compensated or meso form, in addition to the dextro- and levo-rotatory isomers. The case is analogous to that of tartaric acid among the active carbon compounds.
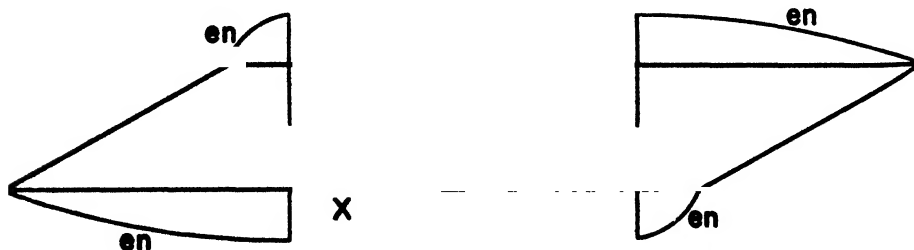
Inactive meso form

Dextro form

Levo form
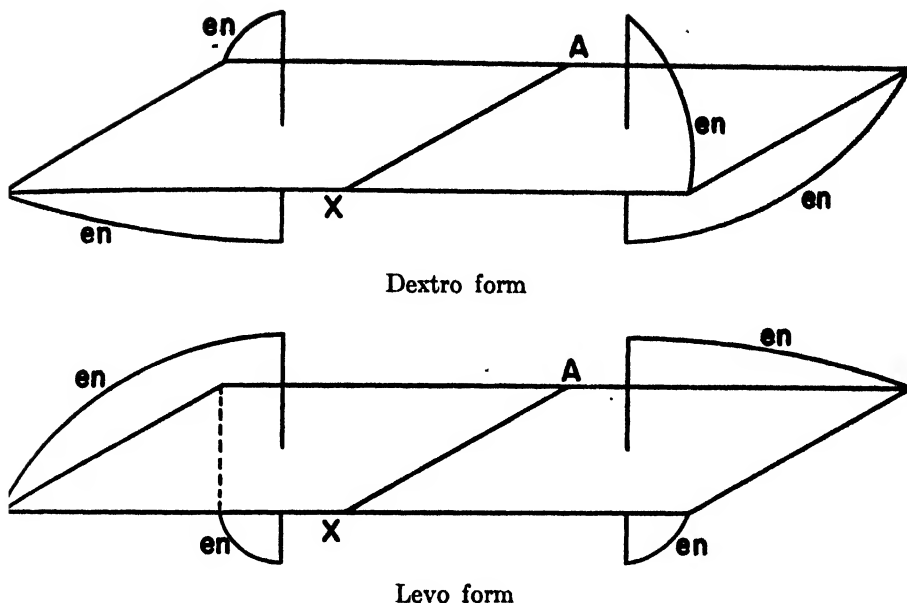
(c) Purely inorganic compounds which exhibit optical activity

In those cases of optical activity which have just been mentioned, the complexes have contained coördinated carbon compounds in the form of chelating groups such as the oxalate radical, ethylenediamine, dipyridyl, etc. It is only natural that the question should arise as to whether optical activity would be displayed by the introduction of chelating groups which are purely inorganic. So far, only two instances have been recorded of the successful resolution of purely inorganic compounds, namely that of Werner (811), in 1914, who resolved the hexoldodecamminecobaltic ion

$$\left[Co\left(\begin{array}{c} HO \\ HO \end{array} Co(NH_3)_4 \right)_3 \right]^{6+}$$
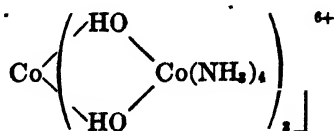
by means of bromocamphorsulfonic acid, and that of Mann (556), in 1933, who resolved the sulfamide compound of rhodium by means of α-phenylethylamine.

In principle the polynuclear compound of Werner is analogous to the trisethylenediaminecobaltic salts, $[Coen_3]X_3$, the difference being that the group

$$\begin{array}{c} HO \\ \diagdown \\ \diagup \\ HO \end{array} Co(NH_3)_4$$

, instead of ethylenediamine, functions as the chelating group.
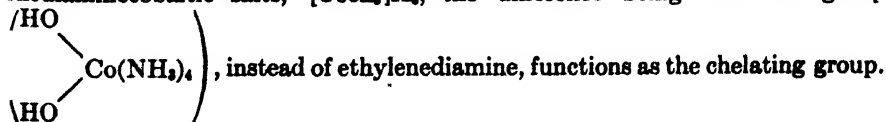
Mann's compound is of the general type $[Men_2AB]$, with only two chelating groups. According to Mann, sulfamide, $SO_2(NH_2)_2$, in coördinating with

rhodium and with platinum, functions as a dibasic acid, $[SO_2(NH)_2]H_2$, to form the compounds $[Rh(SO_2N_2H_2)_2(H_2O)]Na$ and $[Pt(SO_2N_2H_2)_2(OH)(NH_3)]Na$.

4. Coördination isomerism

Under the term "coördination isomerism" Werner lists compounds in which two central atoms, one in the positive complex and one in the negative complex, give rise to isomerism. Examples in which the two central atoms are different are the following: the violet $[Cu(NH_3)_4]^{II}[PtCl_4]^{II}$ and the green $[Pt(NH_3)_4]^{II}$-$[CuCl_4]^{II}$; $[Zn(NH_3)_4]^{II}[PtCl_4]^{II}$ and $[Pt(NH_3)_4]^{II}[ZnCl_4]^{II}$; $[Cren_3]^{III}[Co(C_2O_4)_3]^{III}$ and $[Coen_3]^{III}[Cr(C_2O_4)_3]^{III}$. Examples in which the central atoms are the same but different in valency are: $[Pt(NH_3)_4]^{II}[PtCl_6]^{II}$ and $[Pt(NH_3)_4Cl_2]^{II}$-$[PtCl_4]^{II}$; $[Ptpy_4]^{II}[PtCl_4]^{II}$ and $[Ptpy_2Cl_2]^{II}[PtCl_4]^{II}$. The isomeric pairs have the same empirical composition. The Roman numerals are here used to indicate the net charges of the complex ions.

In connection with compounds of this type, the number of known isomeric forms of certain of the planar compounds exceeds that permitted on the basis of the planar hypothesis. The cause of such anomalies has not yet been fully interpreted. The best known instance is that of the green salt of Magnus, $[Pt(NH_3)_4]$ $[PtCl_4]$, which also exists in an unstable red form. While it has been suggested that the red salt is not Magnus' salt, but is chlorotriammineplatinous chloroplatinite, $[Pt(NH_3)_3Cl]_2[PtCl_4]$, which, like $[Pt(NH_3)_4]$ $[PtCl_3(NH_3)]_2$ and $[Pt(NH_3)_3Cl]$ $[PtCl_3(NH_3)]$, has the same empirical formula, this view is not reconcilable with the work of Drew and Tress (582). As a matter of fact, either the green or the red form of $[Pt(NH_3)_4]$ $[PtCl_4]$ gives rise to grayish pink needles of $[Pt(NH_3)_4]$ $[PdCl_4]$, which are different from the golden brown plates of $[Pt(NH_3)_3Cl]_2[PdCl_4]$ produced from the red $[Pt(NH_3)_3Cl]_2[PtCl_4]$. The formation of the red salt of Magnus is favored, in general, in ammoniacal solutions, in which the triammine compound would be readily converted into the tetrammine compound. Although the individuality of the two forms is assured, the relation between them is not clear.

Other examples of anomalous isomerism exist in the case of the yellow and red forms of $[PtCl_2dipy]$ and in that of the yellow and red forms of $[Pd(NH_3)_2Cl_2]$ and $[Pd(NH_3)_2I_2]$.

5. The "isomeric chlorides" of ruthenium

Another instance of unexplained isomerism, with which Werner brought his book (778) to a close, was that supposed to exist among the chloro compounds of ruthenium.

Claus, the discoverer of ruthenium, prepared (785) two chloro salts of ruthenium to which he assigned the formulas K_2RuCl_5 and K_2RuCl_6. The first was formed when the precipitated oxide of ruthenium, or the volatile tetroxide, was dissolved in hydrochloric acid and treated with potassium chloride; the second, when aqua regia was used. Later (792, 796), it was shown that the supposed K_2RuCl_6 was a nitroso salt, K_2RuCl_5NO. The first salt has, since the time of Claus, passed for K_2RuCl_5, which was considered a pentachlororuthenite. Ef-

forts to oxidize this salt to K_2RuCl_6 have been of no avail. Miolati and Tagiuri (801) reported a monohydrate of K_2RuCl_5.

In 1904 Howe (793) described a new monohydrate of K_2RuCl_5, which differed very markedly from the former salt in properties, especially in stability toward hydrolysis and in being converted into K_2RuCl_6 by the action of chlorine. It was formed from the earlier K_2RuCl_5 by boiling with dilute alcohol in acid solution, and was called an "aquo" salt. The corresponding rubidium and cesium salts were also prepared, as well as similar salts with bromine (794) in the place of chlorine. It was thus thought that there might be an instance of isomerism be- tween these two series of pentachlororuthenites.

The explanation of this anomaly depended upon ascertaining the state of valency of the ruthenium in the two types of compounds, and in determining the composition of the salts, particularly with respect to water. Considerable confusion appeared to exist in ascertaining the state of valency. In reducing ruthenium solutions with zinc, hydrogen sulfide, and other agents, a conspicuous blue color is formed. Claus had regarded the color as that of bivalent ruthenium. Remy and Wagner (319) considered it to be that of univalent ruthenium and based their opinion on its being formed when the valency of the ruthenium in K_2RuCl_5 was reduced two units, as measured by the action of sodium amalgam. Zintl and Zaimis (813) also assumed the presence of univalent ruthenium in the blue solution, basing their view on the potentiometric titration of "$RuCl_3$" with chromous or titanous sulfate, where with one equivalent they obtained a pale yellow solution, while with the next drop the blue began to appear.

Charonnat (505) in 1925 suggested that the true formula for the ordinary pentachlororuthenite is [K_2RuCl_5OH], basing his view on the action of this salt on potassium iodide, and on the formation of the aquo salt by the action of hydrochloric acid on the oxalato compound, $K_3[Ru(C_2O_4)_3]$. Charonnat, however, did not support his idea with details or analyses.

Howe's last paper (693) on the subject concludes that no isomerism exists and that the explanation lies in the fact that Claus' K_2RuCl_5 is in reality $K_2[RuCl_5-OH]$, in which ruthenium is quadrivalent and that the aquo salt $K_2RuCl_5 \cdot H_2O$ is $K_2[RuCl_5H_2O]$, in which ruthenium is tervalent.

D. INNER COMPLEX SALTS

Of the different types of coördination compounds perhaps none interest the analytical chemist more than those which Werner termed inner complex salts.

It will be recalled that the non-electrolyte complexes, such as triacidotriamminecobalt and diacidodiamminepalladium, are formed by the attachment of an equal number of neutral groups and acidic radicals to the central atom. If the neutral group and the acid radical are united in the same molecule as, for example, in the case of glycine, NH_2CH_2COOH, the compounds formed have, in many cases, great stability, very low solubility in water, but high solubility in organic solvents. Non-electrolyte complexes of this kind are included in the term "inner complex salts" and are usually referred to as inner complex salts of the first order. They possess a considerable practical importance in that the forma-

tion of such compounds underlies the action of many of the so-called specific analytical reagents.

Cobaltic oxide reacts with solutions of glycine, forming a mixture of two compounds which are isomeric and have the composition $Co(NH_2CH_2COO)_3$. These compounds are remarkably stable. They may be dissolved without change in concentrated sulfuric acid; their solutions have practically no electrical conductivity; and cryoscopic measurements show that they are undissociated in solution. They represent the two geometrical isomers of trisglycinecobalt.

Glycine also forms inner complex salts with other metals, for example, with 4-coördinate copper. Pinkard, Sharratt, Wardlaw, and Cox (594) obtained cis- and trans-forms of diglycinepalladium.

A second, particularly important class of inner complex salts is that formed by the enolic form of β-diketones, for example, acetylacetone. The enol group is salt-forming, and the ketonic group then coördinates with the metal. The acetylacetonates are typical non-electrolytes. They are practically insoluble in water, but readily soluble in benzene.

The possibility of forming inner complex salts arises whenever donor (amino, thiol, or carbonyl groups) and acidic functions are suitably placed in the same molecule, that is, in 1,4- or 1,5-positions to one another. It is a remarkable and quite unexplained phenomenon that the presence of certain atomic groupings may confer the property of forming inner complex salts more or less specifically with some particular metal, that is, the inner complex salt formed by that metal is characterized above all others by its stability and, as a usual corollary, its insolubility in water.

Of particular interest to the platinum chemist is the atomic grouping of dimethylglyoxime,

$$CH_3C=NOH$$
$$|$$
$$CH_3C=NOH$$
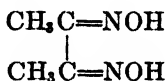
which forms inner complex salts with the 4-coördinate metals, bivalent palladium, bivalent platinum, and bivalent nickel. The discovery of these glyoxime compounds resulted, as was previously mentioned, from the first research made by Chugaev (1) on the platinum metals.

Mann (556) has indicated that chelating groups fall into two classes: (1) Those that can fill all six coördination positions, as can ethylenediamine or the oxalato group; (2) those which, while capable of filling four positions in the 4-coördinate complex, cannot fill more than four coördination positions when introduced into the 6-coördinate complex. Mann's sulfamide belongs to the second class of chelating compounds, and so does dimethylglyoxime. Chugaev showed that although dimethylglyoxime fills completely the four coördination positions about bivalent nickel, palladium, or platinum, compounds of the types $[Codmg_2(NH_3)_2]Cl$, $[Codmg_2(NO_2)_2]NH_4$, and $[Rhdmg_2(NH_3)_2]Cl$ are formed with the 6-coördinate metals cobalt and rhodium, in which it occupies four coördination positions. Herein, undoubtedly, lies the explanation of the clean-

cut analytical separation of bivalent palladium from tervalent rhodium and tervalent iridium by dimethylglyoxime.

If the number of acido groups in the inner complex salt is not equal to the valency of the central atom, the resulting complex will itself be an ion. Werner termed compounds of this type inner complex salts of the second order. For instance, silicon, which is quadrivalent, has a coördination number of six. It forms a complex with three molecules of acetylacetone, [Siac$_3$]Cl, in which one valency of the silicon is unsaturated. The coördination complex thus forms a positive ion. With bivalent cobalt, the coördination number of which is six, the compound is [Coac$_3$]Na, and the complex is negative. In the case of bivalent platinum (coördination number four), the complex portion of the compound [PtCl$_2$ac]K likewise is negative.

The tendency to form inner complex compounds of the second order is shown by organic hydroxy acids, such as tartaric and citric acids, with the result that they are often utilized to mask the usual reactions of the heavy metals.

E. ELECTRONIC INTERPRETATION OF COÖRDINATION

With the enunciation of the theory of the atomic number in 1913, wider interest in coördination compounds was awakened. The coördinate link of Werner took on a new significance and became firmly established as one of the three types of valency now recognized by chemists.

To obtain a clearer picture of coördination than has heretofore been presented in this discussion, it is necessary to review briefly the structure of the atom.

1. Arrangement of the electrons in the atom

The theory of atomic structure which is now almost universally accepted is that due to Rutherford, according to which the atom is built up of a small positively charged nucleus, surrounded by a sufficient number of electrons to render the whole structure electrically neutral. The positive charge of the nucleus of the uranium atom, the heaviest of atoms, is 92 times that of the hydrogen atom, the lightest of atoms. The atomic number of uranium is 92, that of hydrogen, 1.

Two views of the general nature of the electron are held. The first is that the electron in an atom is a minute particle with a mass 1/1840 the mass of the proton, and with a charge equal to $-e$, and moving in an orbit around the nucleus. The second and more recent view is that the electronic charge is not localized in a small element of space, but that there is a probability function which represents its distribution at any given instant. However, the idea of electrons moving in orbits of different energies is a satisfactory approximation for many physical and most chemical purposes.

The proper interpretation of the results of the analysis of the x-ray, ultraviolet, and visible spectra of the elements has given a complete picture of where every electron is situated and what the energy of its orbit is. Four quantum numbers which are necessary in assigning the electrons to their proper positions are: The principal quantum number n; the azimuthal quantum number l; the magnetic quantum number m; and the spin quantum number s. The first division of the

electrons is made according to the principal quantum number n, which can have the values 1, 2, 3, 4, etc. The corresponding shells are often designated K, L, M, N, etc. The azimuthal quantum number can have the values 0, 1, 2, 3, etc. Thus, there is a subdivision of energy levels within the shells K, L, M, N, etc. Electrons with $l = 0, 1, 2, 3$, are called s, p, d, f electrons, respectively. This nomenclature is a survival of an old and empirical notation (s for sharp, p for principal, d for diffuse, f for fundamental) which was based on the appearance of spectral lines caused by electron transitions involving these shells. The two other quantum numbers, m and s, are needed to account satisfactorily for all the observed lines in the spectra of an element.

In addition, a restriction known as the Pauli exclusion principle is likewise needed. According to this principle no two electrons in the same atom can have the same values for the four quantum numbers. This means that every electron in the atom differs from every other electron in total energy, and that there can be as many electrons in each of the shells as there are possible different arrangements of the quantum numbers. It is therefore found that the maximum numbers of electrons in the K, L, M, N, and O shells are 2, 8, 18, 32, and 50, respectively.

It is seen that the K shell, which can contain only two electrons, is completed in helium, and that all elements with more than two electrons have the K shell full. There are only eight possible orbits in the L shell, which is completed in neon, atomic number 10. Like neon, argon, krypton, xenon, and radon have their s and p orbits in their outermost shells completely filled. This configuration, usually called a closed shell, is very stable, and is of interest in the discussion of coördination compounds.

2. Electronic arrangement in the atoms of the metals of the eighth group of the Periodic System

In discussing the coördination compounds of the platinum metals, consideration should also be given to the members of the first triad of the eighth group of the Periodic System. The electronic arrangements of these nine metals, as well as those of krypton, xenon, and radon, may be written in the following abbreviated form, the completed electronic orbits being omitted. The corresponding atomic numbers are given in parentheses.

Fe (26)	Co (27)	Ni (28)	Kr (36)
$3d^6 4s^2$	$3d^7 4s^2$	$3d^8 4s^2$	$4s^2 4p^6$
Ru (44)	Rh (45)	Pd (46)	Xe (54)
$4d^7 5s^1$	$4d^8 5s^1$	$4d^{10}$	$5s^2 5p^6$
Os (76)	Ir (77)	Pt (78)	Rn (86)
$5d^6 6s^2$	$5d^7 6s^2$	$5d^9 6s^1$	$6s^2 6p^6$

It is to be noted that the outermost electronic distributions in iron and osmium are similar, as are also those in cobalt and iridium. Attention is likewise called to the electronic groupings in palladium and platinum, two elements which are

usually regarded as very similar, but which differ markedly in their stable states of electrovalency. ˉ

3. The three types of valency recognized by chemists

The electronic conception of matter gives precision to the coördination theory, since it offers a simple explanation of the three manifestations of valency now recognized by chemists.

The essential feature of the electronic theory of valency is the conception of three types of binding between atoms: namely, electrovalency, covalency, and the coördinate link. In electrovalency an outer electron from one atom or group of atoms is transferred to another atom or group of atoms, the two atoms or groups being then held together by electrostatic attraction. This type of valency is often spoken of as the polar link. Thus, in forming sodium chloride, sodium gives its single outer electron, $3s^1$, to chlorine, and by this exchange the sodium ion acquires the electronic configuration of neon, $1s^2 2s^2 2p^6$, while the chloride ion completes the filling of the $3p$ orbit, $1s^2 2s^2 2p^6 3s^2 3p^6$, and then resembles argon.

In covalency, the non-polar link, the two combining atoms share electrons as in methane, which contains four covalent links. Each of these four links includes two electrons, one contributed by carbon and one by hydrogen, so that in methane carbon has assumed the electronic structure of neon and each hydrogen atom has acquired the two electrons which are characteristic of helium.

The third type of link is the coördinate link, coördinate covalency. This is identical with the covalent link except that both electrons forming a bond come from one of the two atoms which are joined together. This type of combination is exemplified in hexammineplatinic chloride, $[Pt(NH_3)_6]Cl_4$, in which the quadrivalent platinum ion, which differs from radon by twelve electrons, completes its quota of electrons by coördinating with six molecules of ammonia. In this combination each nitrogen atom contributes two shared electrons, so that within the coördination sphere the platinum has acquired the electronic configuration of radon and each nitrogen retains that of neon.

It is to be noted that the driving force in these three types of linking is a tendency on the part of the combining atoms to assume the electronic configuration of the nearest inert gas.

4. Magnetic susceptibility as an aid in examining coördination compounds

One physical method which is used to examine coördination compounds is that which measures their behavior in a magnetic field. This type of measurement affords a means of detecting the presence of singly occupied electron orbits, and such information can be of direct utility in determining the molecular complexity of compounds. It also provides a delicate criterion for the transition from electrostatic to covalent linking in complex salts.

Without going into detail on the subject of magnetism, suffice it to say here that the property of ferromagnetism, which varies with temperature and passes

over into paramagnetism at the Curie point, has its origin in the parallel orientation of molecular magnets over microscopic regions of the solid. The effect is shown by the iron group metals, by some of their compounds, and by Heusler alloys. In the case of iron the magnitude of the effect is very large.

Ionic paramagnetism, which likewise varies with the temperature, is shown by the ions of the transition and rare earth metals, Cu^{2+}, Co^{2+}, Nd^{3+}. The effect is large and has its origin in the resultant spin or orbital angular momentum of incomplete electronic shells.

Metallic paramagnetism, independent of temperature, is shown by the alkali metals, by copper and silver, and by some of the carbides and nitrides. It results from the uncompensated spin of the metallic conduction electrons.

Residual paramagnetism, likewise independent of temperature, results from the uncompensated paramagnetism of complex ions. For example, the polyatomic ions, especially oxyacid ions, of transition elements, such as MnO_4^- and MnO_4^{2-}, show residual paramagnetism.

Diamagnetism, also independent of temperature, is shown by inert gas-like ions, such as Na^+, Br^-, etc., and by complex ions of the transition metals, such as $[Co(NH_3)_6]^{3+}$. Its origin is in the interaction of the magnetic field with closed electronic shells.

The magnitude of diamagnetic effects is small. Paramagnetic substances interact much more strongly with the magnetic field since each molecule or atom behaves as an elementary magnet.

5. Effective atomic number and stability

A particularly interesting aspect of complex formation is the manner in which the attachment of strongly coördinating groups may lead to the stabilization of a valency state, derivatives of which are otherwise unstable. A familiar and striking example of this phenomenon is found in the cobaltammines. In the presence of ammonia, the relative stabilities of the $[Co(NH_3)_6]^{3+}$ and $[Co(NH_3)_6]^{2+}$ ions are so far reversed that oxidation to the first-named state is effected by atmospheric oxygen at room temperature. The same stabilizing effect is produced by the coördination of anions, as is shown by the strong reducing properties of potassium cobaltocyanide. Both the higher and lower valency states of copper may be stabilized by appropriate coördinating groups. The instability of cupric iodide and cupric cyanide is a familiar fact. The iodide $[Cuen_2]I_2$, with one or two molecules of water of crystallization, is stable, with no tendency to revert to the cuprous state. In the case of the corresponding cyanide, stabilization of the bivalent state is not so complete, so that a derivative of both bivalent and univalent copper, $[Cuen_2][Cu(CN)_2]_2$, is obtained, the formation of which may be attributed to the competing effect of the stabilization of the cuprous state in the complex anion. The coördination of acetonitrile, thiourea, or ethylenethiourea stabilizes the cuprous state.

Univalent silver is also stabilized by coördination with sulfur compounds, for example, $[Agetu_4]Cl$ and $[Agetu_3]Br$. The bivalent state of silver is readily

stabilized by coördination, particularly with pyridine derivatives. The complex argentic cations [Agphenan₂]²⁺ and [Agdipy₂]²⁺ are very stable.

The ferrous state, which in simple salts is readily oxidized by atmospheric oxygen, is strongly stabilized by coördination with dipyridyl or *o*-phenanthroline, so that the salts [Fephenan₃]X₂ and [Fedipy₃]X₂ are much more stable than the ferric salts.

The formation of the most stable complex compounds corresponds in certain cases to the acquirement by the central atom of the same "effective atomic number" as the nearest inert gas, a condition which affords a plausible explanation of the stability and properties of such compounds. In this connection three groups are of particular interest to the platinum chemist: namely, the nitrosyl group, the carbonyl group, and the cyanide group. Neutral nitric oxide has one electron more than has carbon monoxide. The formation of a metal nitrosyl compound can be regarded as invoking first the transfer of an electron from the NO group to the metal, followed by coördination of the (NO)⁺ group thereby resulting. The effective atomic number of the metal atom is thereby increased, and its electrovalency, if an ion, is decreased, each by one unit. In an exactly similar way, the coördination of a (CN)⁻ group raises the electrovalency by one unit. The coördination of the carbonyl group does not change the electrovalency of the central atom.

The effective atomic number of the central atom may be arrived at in several equivalent ways. For instance, in ascertaining that of the platinum atom in [Pt(NH₃)₆]Cl₄, the cationic complex may be considered.

$$[Pt(NH_3)_6]^{4+}$$
Pt⁴⁺.............................. 74 electrons
6NH₃ donate...................... 12
Total E. A. N...................... 86 (radon configuration)

In [Pt(NH₃)₂Cl₂]:
Pt²⁺.............................. 76 electrons
2NH₃ donate...................... 4
2Cl⁻ donate...................... 4
Total E. A. N...................... 84 (2 electrons short of radon)

In this method it is necessary to know the state of valency of the central atom, which in the first example is four and in the second, two.

It is not always easy to ascertain with certainty what the state of valency is in compounds such as K₂[RuCl₅NO], K₂[OsCl₅NO], and K₂[Fe(CN)₅NO]. If a solution containing the chloro acid of tervalent ruthenium is treated with nitric acid, the salt which is precipitated by the addition of potassium chloride is K₂[RuCl₅NO]. In this salt, as in K₂[Fe(CN)₅NO], the valency of the central atom is regarded as two.

Perhaps as simple a rule as any in arriving at the effective atomic number, and incidentally, the valency of the central atom, is as follows: Each nitric oxide

molecule transfers one electron to the central atom and donates two; each carbon monoxide molecule donates two electrons; each neutral molecule, such as NH_3, donates two electrons; each CN group withdraws one electron from the central atom and donates two; each chlorine atom likewise withdraws one electron and donates two. In addition, if the central atom is in the anionic complex, electrons equal in number to the unit charges on the complex are added; if the central atom is in the cationic complex, the number is subtracted in totaling the effective atomic number. A few examples may make this clear.

$Ni(CO)_4$	$28 + 8 = 36$	(Kr)	
$Fe(CO)_5$	$26 + 10 = 36$	(Kr)	
$Cr(CO)_6$	$24 + 12 = 36$	(Kr)	
$Mo(CO)_6$	$42 + 12 = 54$	(Xe)	
$Ru(CO)_5$	$44 + 10 = 54$	(Xe)	
$K_2[Fe(CN)_5NO]$	$26 - 5 + 10 + 1 + 2 + 2 = 36$	(Kr)	
$K_2[Ru(CN)_5NO]$	$44 - 5 + 10 + 1 + 2 + 2 = 54$	(Xe)	
$K_2[RuCl_5NO]$	$44 - 5 + 10 + 1 + 2 + 2 = 54$	(Xe)	
$K_2[OsCl_5NO]$	$76 - 5 + 10 + 1 + 2 + 2 = 86$	(Rn)	
$K_3[Fe(CN)_5CO]$	$26 - 5 + 10 + 2 + 3 = 36$	(Kr)	
$K_3[Fe(CN)_5NH_3]$	$26 - 5 + 10 + 2 + 3 = 36$	(Kr)	
$K_4[Fe(CN)_6]$	$26 - 6 + 12 + 4 = 36$	(Kr)	
$K_4[Ru(CN)_6]$	$44 - 6 + 12 + 4 = 54$	(Xe)	
$[Pt(NH_3)_6]Cl_4$	$78 + 12 - 4 = 86$	(Rn)	
$K_2[PtCl_6]$	$78 - 6 + 12 + 2 = 86$	(Rn)	

The foregoing compounds, in which the central metallic atom has assumed the configuration of an inert gas, are found to be diamagnetic. Diamagnetism, apparently, is not confined solely to the full attainment of the inert-gas structure. Compounds in which the effective atomic number of the central metallic atom is two electrons short of the inert-gas configuration are likewise diamagnetic. For example,

$[Pt(NH_3)_2Cl_2]$	$78 - 2 + 4 + 4 = 84$
$[Pd(NH_3)_2Cl_2]$	$46 - 2 + 4 + 4 = 52$
$K_2[Ni(CN)_4]$	$28 - 4 + 8 + 2 = 34$
$K[AuBr_4]$	$79 - 4 + 8 + 1 = 84$

Paramagnetism is associated with unpaired electrons, such as is the case in the following:

$K_3[Fe(CN)_6]$	$26 - 6 + 12 + 3 = 35$
$[Cu(NH_3)_4]Cl_2$	$29 + 8 - 2 = 35$

It is only natural that one interested in the chemistry of the platinum metals should examine the more frequently encountered compounds with respect to the effective atomic number and stability, thus to correlate everyday experience with theoretical guidance.

Chloro salts

$K_2[PtCl_6]$	$78 - 6 + 12 + 2 = 86$ (Rn)
$K_2[PtCl_4]$	$78 - 4 + 8 + 2 = 84$
$K_2[IrCl_6]$	$77 - 6 + 12 + 2 = 85$
$K_3[IrCl_6]$	$77 - 6 + 12 + 3 = 86$ (Rn)
$K_2[OsCl_6]$	$76 - 6 + 12 + 2 = 84$
$K_3[OsCl_6]$	$76 - 6 + 12 + 3 = 85$
$K_2[OsCl_5NO]$	$76 - 5 + 10 + 1 + 2 + 2 = 86$ (Rn)
$K_2[PdCl_6]$	$46 - 6 + 12 + 2 = 54$ (Xe)
$K_2[PdCl_4]$	$46 - 4 + 8 + 2 = 52$
$K_2[RhCl_6]$	$45 - 6 + 12 + 2 = 53$
$K_3[RhCl_6]$	$45 - 6 + 12 + 3 = 54$ (Xe)
$K_2[RuCl_6]$	$44 - 6 + 12 + 2 = 52$
$K_3[RuCl_6]$	$44 - 6 + 12 + 3 = 53$
$K_2[RuCl_5NO]$	$44 - 5 + 10 + 1 + 2 + 2 = 54$ (Xe)

In general, it may be remarked that those compounds in which the effective atomic number of the central atom is odd are unstable. The tendency of chloro salts of quadrivalent iridium is to reduce to the tervalent form when dissolved. When chloro salts of quadrivalent palladium are dissolved in water, chlorine is liberated and the palladium atom becomes bivalent. Chloro salts of quadrivalent rhodium have never been prepared, the effective atomic number of rhodium in the tervalent state reaching the inert-gas number. In the case of tervalent ruthenium and osmium, the coördination of a nitrosyl group, with its transfer of one electron, completes the inert-gas configuration. As mentioned earlier, the nitroso complex of ruthenium is extremely stable.

In the analytical procedure involving the separation of base metals from platinum, iridium, rhodium, and palladium, these four metals are first converted to complex nitrite compounds. The compounds formed are:

$Na_2[Pt(NO_2)_6]$	$78 - 6 + 12 + 2 = 86$ (Rn)
$Na_3[Ir(NO_2)_6]$	$77 - 6 + 12 + 3 = 86$ (Rn)
$Na_3[Rh(NO_2)_6]$	$45 - 6 + 12 + 3 = 54$ (Xe)
$Na_2[Pd(NO_2)_4]$	$46 - 4 + 8 + 2 = 52$

At an alkalinity of pH 8 these compounds are stable in a boiling solution. At an alkalinity approaching pH 10 the palladium compound begins to decompose, with the precipitation of a brownish deposit, and at higher alkalinities the decomposition is undoubtedly complete. The nitrite complexes of platinum, iridium, and rhodium were observed not to decompose at alkalinities of pH 12 to 13, and they are probably stable at even higher alkalinities.

Further discussion of the electronic interpretation of coördination leads naturally to hybridized orbits and quantum mechanics, subjects which are beyond the simple scope of this presentation. It is therefore recommended that the reader consult the two papers by Pauling (806) for his discussion of the nature of the chemical bond.

IX. The Literature

For the sake of convenience, the references here given are first of all divided into two groups. Those in group A are to papers which were published in the period from 1915 to 1940, and which deal with the inorganic and analytical chemistry of the platinum metals. One exception to this is made by including Chugaev's first research on the platinum metals (reference 1), because of its special significance. Within the group, the papers are arranged by nationality of origin and, so far as possible, by assembling them according to the leading authors. Under each such author, the papers are listed in chronological order. In locating the original papers and identifying them with the references, it was found that most of them were available in the Library of the National Bureau of Standards. Each paper not contained in the Bureau's library is marked with an asterisk.

The references in group B are to other publications that were necessary in the discussion of the subject matter of the paper.

A. REFERENCES TO THE PERIOD 1915 TO 1940

Russian contributions

From 1921 to 1935 practically the entire Russian literature on the platinum metals appeared in a journal created specifically for the purpose. It is known as *Annales de l'institut de platine (Leningrad)*. Twelve numbers of this journal appeared. Beginning with 1936 a new journal, entitled *Annales du secteur du platine, Institut de chimie générale (Moscow)*, displaced the former one but began its issues with No. 13 of the series. In these journals the papers are in the Russian language. In the *Comptes rendus* and in the *Bulletin of the Academy of Sciences* many of the papers are in English, German, or French, thereby making them more accessible to the average reader. Not all of the papers contained in these two journals are listed here. Such others as may interest the reader may be readily found in them.

The transliteration of the Russian names used here is in most cases that followed by *Chemical Abstracts*.

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VII. Reports of the Committee on Analysis

The Committee on Analysis of the Platinum Institute consisted of S. F. Zhemchuzhniĭ, O. E. Zvyagintzev, B. G. Karpov, V. V. Lebedinskiĭ, N. I. Podkopaev, A. T. Grigoriev, and N. S. Kurnakov. It made its first report in 1926, and a second in 1932.

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THE NITROPARAFFINS

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CONTENTS

I. INTRODUCTION

In May, 1940, the first production of nitroparaffins on an industrial scale occurred at the plant of the Commercial Solvents Corporation, Peoria, Illinois. The process involved the newly invented vapor-phase nitration technic, which was first employed by Hass, Hodge, and Vanderbilt (132, 133, 134) at Purdue University, and which has been in active development since the autumn of 1930. By nitrating the propane of natural gas and of petroleum, which is available in

practically unlimited quantities, the first four nitroparaffins are produced: nitromethane, nitroethane, 1-nitropropane, and 2-nitropropane. The nitration of any of the volatile higher or lower homologs of the paraffinic or naphthenic series can be accomplished by the same general procedure. From our most inexpensive organic raw materials it is thus possible to obtain nitro derivatives by the action of the acid which the researches of Haber and Ostwald have placed among our most available and cheapest inorganic reagents. It is therefore an appropriate time to review[1] the syntheses, properties, uses, and reactions of the nitroparaffins and their immediate derivatives.

II. THE VICTOR MEYER REACTION

In 1872 Meyer and Stüber (271) reported that the reaction between amyl iodide and silver nitrite had yielded nitropentane and amyl nitrite. At that time the aromatic nitro derivatives were already of substantial importance, since Mauvein had been made by Perkin sixteen years before and the aniline dye industry was in active development. It is not surprising, therefore, that this first synthesis of a nitroparaffin[2] should have aroused general interest and resulted in the publication of a considerable number of papers. The Victor Meyer reaction has been reviewed and extended by Reynolds and Adkins (329), so that no detailed discussion need be given here. It should be mentioned, however, that it has been found suitable for producing not only nitroparaffins but also polynitroparaffins (55), nitroalcohols (81), nitroölefins (56, 260), nitroethers, nitroketones, and many other aliphatic nitro compounds.

Salts of α-halocarboxylic acids react similarly even with sodium nitrite and yield salts of α-nitrocarboxylic acids which readily decompose, producing nitroparaffins and metallic bicarbonates. Kolbe (202) reported this reaction only five months after Meyer and Stüber's first announcement of the nitroparaffins.[3]

The reasons for the wide differences between the ratios of organic nitrite and nitro derivative obtained from various organic halides and metallic nitrites are still obscure. Reynolds and Adkins have postulated that an addition complex is formed between the two reagents and that every constituent of the complex is thus in a position to influence the further course of the reaction to yield either nitrite or nitro compound. It is probably of significance that nitrites readily rearrange to nitro derivatives at elevated temperatures (287). The yield may therefore fluctuate with the amount of local overheating.

III. MISCELLANEOUS METHODS OF INTRODUCING THE NITRO GROUP INTO ALIPHATIC COMPOUNDS

(a) A primary amine may be oxidized directly to a nitroparaffin. Thus methylamine, ethylamine, tert-butylamine, and benzylamine have been oxidized to the corresponding nitro compounds. Bamberger and Seligman (18) give the following equations:

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[1] Brief reviews of this general nature have recently appeared by Hurd (115), Ellis (93, 94), Hass (131), and Gabriel (107, 108). Because of the limitations of time and space and the very extensive literature, the present article is by no means exhaustive.

[2] Chloropicrin and bromopicrin had been made much earlier (365, 366).

[3] For a recommended laboratory procedure, see Organic Syntheses (291).

$$CH_3NH_2 \rightarrow CH_3NHOH \rightarrow CH_2=NOH \nearrow HC(OH)=NOH$$

$$\searrow$$

$$\downarrow$$

$$H_2O + HCN \quad CH_2NO_2H \rightarrow CH_3NO_2$$

$$\downarrow$$

$$HCOOH$$
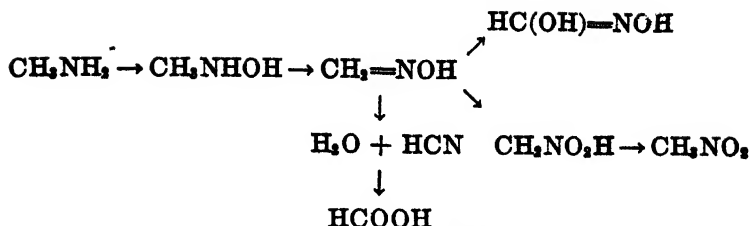
(b) Halonitroparaffins may be treated with zinc alkyls to replace one, two, or three halogen atoms with alkyl groups. Bevad (32, 33) obtained tertiary nitrobutane by the action of dimethylzinc upon chloropicrin.

(c) By using a metallic derivative of an aci-nitroparaffin and an alkyl halide, one obtains either a nitronic ester or a higher nitro derivative.

$$R_2C=NO_2M^* + R'X \rightarrow R_2C=NO_2R' + MX$$

$$\searrow$$

$$R_2CR' + MX$$

$$\underset{NO_2}{|}$$
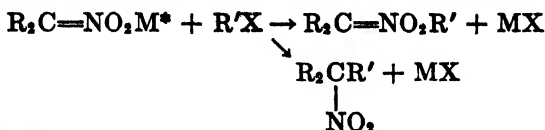
* (M = K, Na, or Ag)

This reaction has recently been reviewed and extended by Brown and Shriner (57), Thurston and Shriner (378), and Weisler (398). The nitronic esters are frequently instable, decomposing as follows:

$$\overset{O}{\underset{\uparrow}{R_2C=N}}-OCH_2R' \rightarrow R_2C=NOH + R'CHO$$
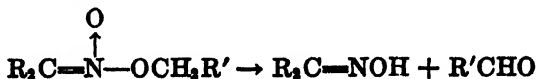
As in the Victor Meyer reaction, very different ratios of nitro derivative to by-product are observed, depending upon the particular reactants. There is some evidence (398) that high yields of nitro derivative correlate positively with the lability of the halogen atom. In the related synthesis of the dinitroparaffins (cf. section VI) by the reaction

$$R_2C=NO_2Na + R_2\overset{X}{\underset{|}{C}}NO_2 \rightarrow R_2C\underset{NO_2}{\overset{|}{\rule{1cm}{0.4pt}}}CR_2 + NaX$$
$$\qquad\qquad\qquad\qquad\qquad \underset{NO_2}{|}\quad\underset{NO_2}{|}$$
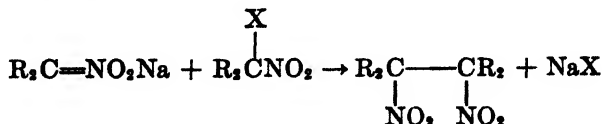
best yields were obtained with iodides and poorest with chlorides; these results are, of course, in harmony with the above generalization. Alkyl sulfates are also suitable as alkylating reagents for nitroparaffins (11).

(d) An alkyl nitrite may be caused to rearrange to form a nitroparaffin (111, 287). When ethyl nitrite and hydrogen are passed over finely divided nickel or nickelized asbestos, amines are formed. This reaction is ascribed to preliminary rearrangement of the nitrite to nitroparaffin.

(e) Certain olefins will add nitrogen tetroxide to yield dinitroparaffins. The reactions between olefins and the oxides of nitrogen are complex and quite worthy of a separate review; apparently either or both of the doubly bound

carbon atoms may form carbon–oxygen or carbon–nitrogen linkages. 2,3-Dimethyl-2-butene reacts as follows:

$$(CH_3)_2C{=}C(CH_3)_2 + N_2O_4 \rightarrow (CH_3)_2\overset{\displaystyle NO_2}{\underset{\displaystyle |}{C}}{-}{-}\overset{\displaystyle NO_2}{\underset{\displaystyle |}{C}}(CH_3)_2$$
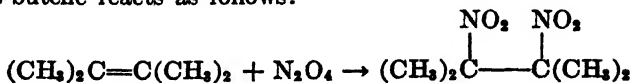
Tetrachloroethylene and tetrabromoethylene react analogously to yield 1,2-dinitrotetrachloroethane and 1,2-dinitrotetrabromoethane (7, 41). Haitinger (122) treated isobutylene with concentrated nitric acid and obtained the compound $C_4H_2N_2O_4$, perhaps by the same reaction. Although its structure is uncertain, the production of the same compound by the liquid-phase nitration of a petroleum distillate indicates that it may be a dinitroparaffin.

IV. LIQUID-PHASE NITRATION OF SATURATED HYDROCARBONS

In spite of the fact that Mills (273) had nitrated chloroform in a sealed tube before the first nitroparaffin had been reported, eight years elapsed between the announcement of the Victor Meyer reaction and the first report of the production of a nitroparaffin by the direct nitration of a hydrocarbon. Beilstein and Kurbatov (24, 25) had observed that fractions of Caucasian petroleum are readily nitrated to yield nitro derivatives of cycloparaffins. A fraction of American petroleum boiling at 95–100°C. had a density between that of a paraffin and a cycloparaffin, and selective nitration was used in a successful effort to purify it from naphthenic components. The nitro derivative boiled for the most part from 193° to 197°C. and had a composition corresponding to the formula $C_7H_{15}NO_2$. On the basis of present knowledge it must have been a mixture of nitroheptanes in which 2-nitroheptane and the 3- and 4-nitro derivatives predominated.

This work was followed by a large number of articles (93) describing the nitration of paraffins and naphthenes and more complex mixtures; these materials range from pentanes to the residues from the distillation of petroleum. The following generalizations have emerged from these researches:

(a) Tertiary hydrogen atoms in either paraffins or cycloparaffins are most rapidly replaced, secondary hydrogen atoms react more sluggishly, and primary hydrogen atoms most slowly. The only apparent exception to this generalization is found in the work of Worstall (413, 418), who reported exclusively primary nitro derivatives from hexane, heptane, octane, nonane, and decane. Worstall refluxed his reagents at atmospheric pressure and therefore used rather low temperatures, which necessitated prolonged reaction. It seems likely that the secondary nitroparaffins were selectively attacked by the nitric acid, and that this phenomenon accounts for both the high proportion of polynitro derivatives and the preponderance of primary nitroparaffins in the mononitrated products. Henry (158) showed later that at least part of Worstall's identifications were in error.

(b) Reaction is slow but yields and conversions are increased at higher temperatures. For example, the report of a yield of 60 per cent in the nitration of n-hexane (413) was a misprint; the yield was actually 6.0 per cent. This resulted from several days' refluxing in an open vessel. Yields as high as 70 per cent were obtained with nonane which, of course, has a much higher re-

fluxing temperature even in the presence of nitric acid. The product was a mixture of mono- and poly-nitro derivatives. By employing the sealed-tube technic, Konovalov found that, although a low yield was obtained at 115–120°C. with *n*-hexane, and nitric acid of density 1.155 (206), increase of the temperature to 140°C. and the use of more dilute nitric acid (density 1.075) resulted in a 60 per cent yield of nitrohexanes.

(*c*) A great deal of oxidation accompanies the nitration. Since the nitric acid is largely reduced to elementary nitrogen, this constitutes an economic loss. The contrast between the vapor-phase reaction (see section V), which yields almost no elementary nitrogen, and the liquid-phase nitration is presumably attributable to the effect of mineral acids upon nitroparaffins. This topic is discussed in more detail in section X, but it may be mentioned here that primary nitroparaffins yield carboxylic acids and salts of hydroxylamine. Hydroxylammonium nitrate decomposes at 100°C., yielding water, nitrogen, and oxygen (255).

(*d*) Large quantities of polynitroparaffins are formed. This may be caused by the fact that nitric acid and saturated hydrocarbons are immiscible, while the mononitro derivatives are much more soluble in the acid and are there presumably oxidized, nitrated, and hydrolyzed.

(*e*) The sulfuric acid–nitric acid mixture used for nitrating aromatic hydrocarbons is not suitable for paraffins. Primary nitroparaffins are quickly hydrolyzed by hot sulfuric acid, and the secondary and tertiary isomers are converted to brown tars. Markovnikov (244) has found that, to attack alkanes, mixtures of nitric and sulfuric acids require a higher temperature than nitric acid. Thus, while many paraffins with tertiary hydrogen atoms are attacked appreciably by nitric acid at 20°C., these same ones require a temperature of 43° to 85°C. with mixed acid. The sulfuric acid probably decreases the small mutual solubility of nitric acid and alkanes. Cycloparaffins react with mixed acid to yield dicarboxylic acid without loss of carbon atoms. In this connection it is interesting to note that highly methylated aromatic hydrocarbons are nitrated on the ring with mixed acid and on a methyl group with dilute nitric acid alone.

(*f*) In order to promote miscibility between nitrating agent and hydrocarbon, such reagents as nitric–acetic acid mixtures, benzoyl nitrate, and acetyl nitrate have been used. Ethyl nitrate and sodium ethoxide (409) are effective with compounds containing active hydrogen. Aside from the explosion hazards involved in employing such compounds as ethyl or acetyl nitrate, these reagents suffer from the disadvantage that they are gradually attacked. An attempt to nitrate isobutane in this laboratory (133) in the presence of acetic acid resulted in substantial oxidation of the acetic acid. Haines and Adkins (120) reported the rapid nitration of *n*-heptane at 0°C. by the action of nitrogen pentoxide. The products were rather involatile (b.p. 130–180°C. or higher at 25 mm.) and were not identified. They may have been polynitro derivatives.

(*g*) Aluminum nitrate has been recommended as a catalyst for liquid-phase nitrations. Work in this laboratory (83) has shown that the principal effect of the aluminum nitrate is to raise the boiling point of the nitric acid. The increased temperature of reflux results in more rapid nitration but sodium nitrate has approximately the same effect.

After Emil Fischer (99) had shown that nitromethane is an excellent solvent for cellulose nitrate, cellulose acetate, and mixtures thereof, Hopkins (169) disclosed the nitration (catalyzed by aluminum nitrate) of volatile petroleum fractions from about C_6 to C_8, and Hopkins and Buc (170) described the use of the nitrated derivatives in admixture with alcohol as cellulose ester solvents. So far as is known, the process and product never reached commercial production. This may have been a result of the decreased dilution ratios of nitroparaffins with six or more carbon atoms and the disparity in the evaporation rates of ethanol and these nitro derivatives which would have caused separation during drying of the lacquer film.

The liquid-phase nitration of alkanes has recently been investigated by Stevens and Schiessler (367), who found that the 3-nitro-3-methyloctane obtained from *l*-3-methyloctane is optically active. The mechanism therefore does not involve free radicals. The fact, reported by Markovnikov (245), that no rearrangement occurs in the nitration of neohexane is in line with Whitmore's generalization (402) that removal of a positive atom from a neo structure does not cause rearrangement.

The nitration of haloparaffins in the liquid phase has been reported. Thus, chloropicrin may be obtained by the direct nitration of chloroform (273). Dănăilă and Soare (76) reported a 58 per cent yield of chloropicrin when equal volumes of chloroform and nitric acid (density 1.52) were heated at 140–150°C., under pressure for 3 hr., and Konovalov reported that 1-chloro-2-methyl-2-nitropropane constituted 95 per cent of the nitrated product in the nitration of isobutyl chloride (210, 211, 212).

V. VAPOR-PHASE NITRATION

The vapor-phase nitration process is an outgrowth of an attempt to nitrate isobutane. Almost all of the previous liquid-phase nitrations had indicated that a tertiary hydrogen atom is substituted with ease but that primary hydrogens are attacked only to a small extent (see section IV). Since isobutane contains only one tertiary hydrogen atom, the others being primary, it seemed to be uniquely suitable for yielding large amounts of the mononitro derivative. Its nitration had not been reported, and was therefore undertaken. Because of the low boiling point (−12°C.) of isobutane, the sealed-tube technic was employed and the first experiment was conducted at 115°C. When substantially no reaction was observed, the temperature was increased to 150°C. and a smooth nitration was obtained within approximately 15 min. The product was the expected tertiary nitrobutane in a high state of purity. It proved to be free from the lachrymal effects previously noted (30) in a sample made from chloropicrin and dimethylzinc and to have a melting point (25.5°C.) slightly higher than previously reported (24°C.). The conversion, however, was only 22 per cent. A similar experiment with normal butane gave an equally good nitration, indicating that the unique structure of isobutane is not a crucial factor in the reaction.

In attempting to carry out the nitration upon a larger scale, a stainless-steel bomb was used successfully, but it is evident that at 150°C. isobutane (critical

Nitration products of isopentane

Substitution of H

$$O_2NC-C-C + C-C-C + C-C-C + C-C-C-NO_2$$

Fission between C_1 and C_2

$$C-NO_2 + C-C-C-C$$
$$NO_2$$

Fission between C_2 and C_3

$$C-C + C-C-NO_2$$
$$NO_2$$

Fission between C_3 and C_4

$$C-NO_2 + C-C-C-NO_2$$

temperature 134°C.) is in vapor phase and the flow method has very great advantages in controlling such reactions. A vapor-phase nitrator was therefore constructed to operate at substantially atmospheric pressure. The great decrease in concentration resulting from the change from sealed-tube pressures to those of the flow apparatus slowed the reaction and necessitated an increase in temperature. Nitration has been obtained under these conditions at temperatures from 248° to over 600°C. but the range 400° to 450°C. is most generally suitable.

When the product was examined it was found to differ greatly from that obtained in the sealed tube. Instead of the crystalline tertiary nitrobutane, a liquid was obtained which contained relatively little of the tertiary derivative and consisted predominantly of 1-nitro-2-methylpropane with considerable amounts of 2-nitropropane and nitromethane. This work, together with subsequent nitrations of ethane, propane, butane, pentane, and isopentane, has led to the following generalization: When a paraffin is nitrated in the vapor phase at high temperatures, all of the mononitro substitution products are obtained which could result if we conceive of the nitro group as capable of substituting either any hydrogen atom or any alkyl radical present in the hydrocarbon. Thus 2-methylbutane (isopentane) yields 1-nitro-2-methylbutane, 2-nitro-2-methylbutane, 3-nitro-2-methylbutane, and 4-nitro-2-methylbutane by substituting any one of the various hydrogen atoms, and nitromethane, nitroethane, 2-nitropropane, 2-nitrobutane, and 1-nitro-2-methylpropane by substituting alkyl groups.

This reaction was formerly believed to have a free-radical mechanism (236), but this hypothesis seems to be incapable of explaining the large quantity of nitromethane (up to 27 per cent of the nitrated product) obtained when ethane is nitrated. The ethyl radical does not decompose to form any product having a single carbon atom.

R. H. Ewell (96) has suggested that hydrocarbons and nitric acid may form addition complexes which decompose, yielding alcohols and lower nitroparaffins. With ethane, for example, two complexes would be possible, as represented by the following diagrams:
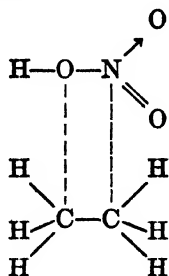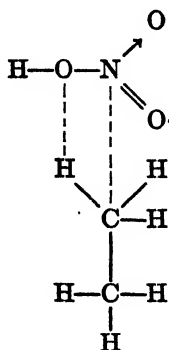
I   II

Compound I would undergo fission, yielding nitromethane and methanol; compound II would yield nitroethane and water.

One deduction from this mechanism is that for every molecule of nitroparaffin formed by C—C fission (i.e., having fewer carbon atoms than the hydrocarbon flowing into the reaction tube), a molecule of alcohol is produced. Qualitatively, alcohols are present in the products of the nitration reaction. Since they are not stable under the nitration conditions, being rather easily oxidized by nitric acid, and since they may in part be formed by direct oxidation of the hydrocarbon, a quantitative comparison is difficult or impossible.

Another prediction of this mechanism is that the 2-nitrobutane formed by the nitration of optically active 3-methylhexane will itself be optically active. This prediction is now in the process of being checked (61).

The addition-complex mechanism is entirely in harmony with the results obtained by Stevens and Schiessler (367) in liquid-phase nitration (*cf.* section IV).

The vapor-phase nitration process does not yield dinitroparaffins when carried out at temperatures of 248°C. or above with either nitric acid or nitrogen dioxide as the nitrating agent (86). Even when nitroparaffins are used as reactants, they are pyrolyzed and oxidized but not nitrated (236). Urbánski and Slon (384), working at 200°C., reported the formation of dinitroparaffins; while their identifications are not too conclusive, it is quite possible that the lower temperature used by them caused this difference. Dorsky's work (86) has shown that over the temperature range 248° to 600°C. nitrogen dioxide and nitric acid yield the same products, although the yields per mole of nitrating agent are higher when nitric acid is used. One reason for the difference in yield can be seen if the following equations represent the two reactions:

$$RH + HONO_2 \rightarrow RNO_2 + H_2O$$

$$RH + 2NO_2 \rightarrow RNO_2 + HNO_2$$

or

$$2RH + 3NO_2 \rightarrow 2RNO_2 + NO$$
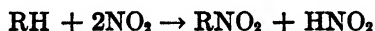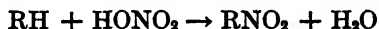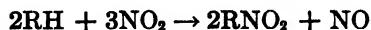
One and one-half or 2 moles of nitrogen dioxide are necessary to do the work of 1 mole of nitric acid.

The effect of increased temperature upon the vapor-phase nitration reaction is to increase (*1*) its velocity, (*2*) the production of primary nitroparaffins at the expense of secondary and tertiary isomers, and (*3*) the yield of fission products. Conversions[4] are surprisingly constant over a wide temperature range when the exposure time and temperature are carefully matched. If one plots conversion against temperature at constant exposure time, a curve is obtained which rises, passes through a maximum, and declines (159). Temperatures below the optimum are too low for completion of the reaction, while those higher than the optimum result in too much pyrolysis of the nitroparaffins. The

[4] By "conversion" is meant the moles of nitroparaffin times 100 divided by the moles of nitric acid passing through the reactor.

importance of this phenomenon is illustrated by the fact that in the commercial nitration of propane, the temperature is controlled to within $\pm 1°F$.

The effect of higher pressure is to increase greatly the rate of the reaction without, usually, greatly affecting the conversion. The catalysts so far studied all accelerate the competing oxidation reaction at the expense of the nitration. When the reaction was transferred from glass into stainless steel, conversions were lowered and became unreproducible. The cause is believed to be a film of metallic oxides, the effect of which Hodge and Swallen (163) showed could be eliminated by the continuous introduction of a small quantity of sodium or potassium nitrate into the reactor to poison the unwanted catalyst.

Under favorable conditions, approximately 40 per cent of the nitric acid passed through the reactor forms nitroparaffins. The remainder functions as oxidizing agent, being reduced almost exclusively to nitric oxide. Alcohols, carboxylic acids, aldehydes, ketones, carbon monoxide, carbon dioxide, and water are thus formed in various quantities. In the commercial plant the nitric oxide is separated from other reaction products and excess unchanged hydrocarbon and is reoxidized to nitric acid. Thus, eventually more than 90 moles of nitroparaffin can be produced for each 100 moles of nitric acid consumed. A study was made of the effect of excess hydrocarbon upon the conversion. The curve obtained when moles of hydrocarbon per mole of nitric acid were plotted against conversion did not extrapolate to 100 per cent conversion at infinite ratio of hydrocarbon to nitric acid. This apparently means that oxidation accompanies and does not merely follow the nitration reaction, i.e., the nitric acid oxidizes the hydrocarbon as well as the nitroparaffin. This conclusion has subsequently been verified by the isolation of 1-propanol and 2-propanol as byproducts of the nitration of propane (162).

As might be expected, methane requires a higher temperature and/or longer exposure time than its homologs and gives a smaller conversion. This is the reason for the failure of the first attempt to nitrate methane in this laboratory. Landon (218, 219), of the research staff of the Hercules Powder Company, has reported the successful nitration of methane; this has been confirmed at Purdue University (54). Ethane is somewhat more easily nitrated, propane still more easily, and little difference is shown by the hydrocarbons above propane.

The nature of the hydrocarbon apparently has less influence upon the course of the vapor-phase nitration reaction than it does with liquid-phase operation. This is to be expected, since reactions are generally less selective at higher temperatures; those having lower activation energies occur more rapidly at low temperatures than competing reactions with higher activation energies; the latter, however, have higher temperature coefficients and hence are favored by temperature increases. A comparison of the nitration of hendecane in the vapor phase and in the liquid phase (83) showed that higher conversions are obtained under the former conditions even with this relatively involatile hydrocarbon.

The nitration of cycloparaffins in the vapor phase has been comparatively

little studied. Cyclohexane is easily nitrated (295) to the mononitro derivative, and there is no doubt that the reaction is as widely applicable in this series as with the alkanes.

When Oleszko and McBee (289) nitrated isobutyl chloride in the vapor phase at 330–340°C., the products obtained were 1-chloro-2-methyl-3-nitropropane, 1-chloro-2-methyl-2-nitropropane, 1-chloro-2-methyl-1-nitropropane, 1-chloro-2-nitropropane, and nitromethane. The absence of monochloronitromethane and of 2-nitropropane is interesting and indicates once more that the reactions of paraffins are more readily predicted than those of the monochloroparaffins.

The vapor-phase nitration of other organic compounds represents a field which has hardly been touched. Treatment of acetic, propionic, butyric, and isobutyric acids with nitric acid at 400°C. yielded practically nothing but unchanged acids, carbon dioxide, water, and nitric oxide (236). Tetraethyllead yielded lead nitrate, ethyl nitrate, and nitroethane. Benzene forms nitrobenzene with ease, but the method (237, 406) probably is not capable of competing economically with the liquid-phase reaction in this instance. Toluene likewise yields nitrobenzene, benzaldehyde, and probably phenylnitromethane, when subjected to vapor-phase nitration (352).

This last reaction recalls the formation of tetranitromethane in the liquid-phase nitration of toluene reported by Gärtner (110). Numerous other compounds have also yielded nitro derivatives of methane when subjected to liquid-phase nitration; the list includes acetylene, acetic anhydride (292), and glycerol (75). Datta and Chatterjee (77) have shown that a great variety of organic materials yield chloropicrin and other chloronitro derivatives of methane when treated with aqua regia.

VI. SYNTHESIS OF ALIPHATIC POLYNITRO COMPOUNDS

(a) The addition of nitrogen tetroxide to olefinic double bonds has already been mentioned (see section III).

(b) Fraser and Kon (102) have reported the condensation of nitromethane with acetone, 2-butanone, 2-pentanone, 3-pentanone, and cyclohexanone. Except for the last, dinitroparaffins were formed by the reaction illustrated below for acetone:

$$CH_3COCH_3 + 2CH_3NO_2 \rightarrow (CH_3)_2C(CH_2NO_2)_2$$
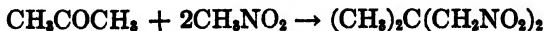
Cyclohexanone with nitromethane, nitroethane, or 1-nitropropane yielded the corresponding nitroalcohols 1-nitromethylcyclohexanol, 1-α-nitroethyl-cyclohexanol, and 1-α-nitropropylcyclohexanol.
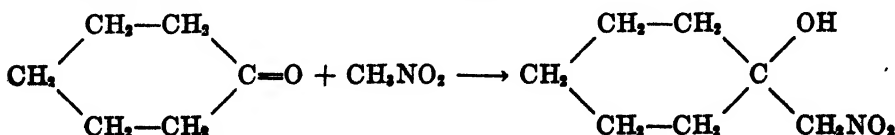
Cyclopentanone yielded the nitroölefin when treated with nitromethane.

$$
\underset{\substack{CH_2-CH_2}}{\overset{\substack{CH_2-C=O}}{CH_2}} + CH_3NO_2 \quad \underset{\substack{CH_2-CH_2}}{\overset{\substack{CH_2-C\overset{OH}{\diagdown}CH_2NO_2}}{CH_2}} \bigg| \longrightarrow
$$

$$
\underset{\substack{CH_2-CH_2}}{\overset{\substack{CH_2-C=CHNO_2}}{CH_2}}
$$
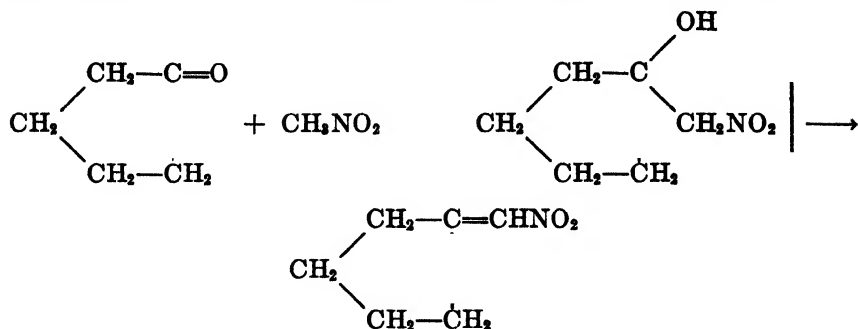
Piperidine and other basic substances were employed as catalysts.

Three chemists at different times, either in this laboratory or at the Commercial Solvents Corporation, have attempted to repeat the work of Fraser and Kon, but with negligible success. By modifications of the conditions for the reaction, Bourland and Larrison have recently been able to achieve these syntheses with satisfactory yields and conversions (48, 221). No explanation of this divergence of results has occurred to us.

(c) A quite analogous reaction with aldehydes has been reported by Heim (143), who condensed 2 moles of phenylnitromethane with 1 mole of benzaldehyde to obtain 1,3-dinitro-1,2,3-triphenylpropane.

$$
2C_6H_5CH_2NO_2 + C_6H_5CHO \qquad \underset{\substack{NO_2 \ H \ NO_2}}{C_6H_5CH-\overset{C_6H_5}{\underset{}{C}}-CHC_6H_5}
$$
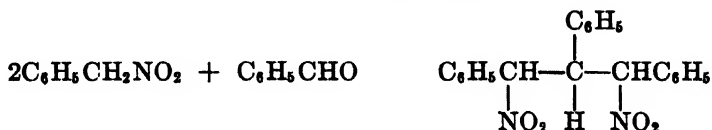
(d) Secondary nitroparaffins, when treated with 1 mole of alkali and 0.5 mole of halogen, yield dinitroparaffins by the following reactions (353):

$$
R_2CHNO_2 + NaOH \longrightarrow R_2C=NO_2Na + H_2O
$$

$$
R_2C=NO_2Na + Cl_2 \longrightarrow R_2CClNO_2 + NaCl
$$

$$
R_2CClNO_2 + R_2C=NO_2Na \longrightarrow \underset{\substack{NO_2 \ NO_2}}{R_2C-CR_2} + NaCl
$$
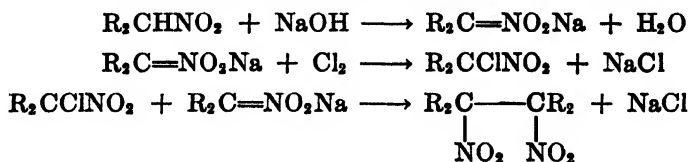
The yields originally reported for the conversion of 2-nitropropane to 2,3-dimethyl-2,3-dinitrobutane were 9 per cent when chlorine was the halogen used, 29 per cent with bromine, and 43 per cent with iodine. Recently this synthesis was repeated (171) in this laboratory with the more nearly pure 2-nitropropane now available from the Commercial Solvents Corporation. 2-Bromo-2-nitropropane gave an 80 per cent yield and 2-chloro-2-nitropropane a 50 per cent yield with the sodium derivative of 2-nitropropane. When either the halonitro compound or the sodium derivative was prepared from a primary nitroparaffin, a zero yield of dinitroparaffin was obtained. Adding a little

nitroethane to the 2-nitropropane used greatly lowered the yield. Nitroethane and 2-nitropropane boil at 114° and 120°C., respectively, and the 2-nitropropane used by Seigle and Hass doubtless contained nitroethane.

Similar reactions have been reported for aliphatic compounds having aromatic substituents. With these compounds even derivatives of primary nitro paraffins react successfully. Thus, Nenitzescu and Isăcescu (285) treated the sodium derivative of phenylnitromethane with iodine and obtained 1,2-dinitro-1,2-diphenylethane.

(e) Angeli and Alessandri (6) reported that the silver salt of nitroethane decomposes spontaneously, yielding 2,3-dinitrobutane. The reaction seems to be general, since the silver salt of a nitropentane reacted similarly to give a dinitrodecane and the silver salt of phenylnitromethane (57) gave 1,2-dinitro-1,2-diphenylethane. Bevad and Pirinsky (40) reported that a similar reaction occurred on treating a *sec*-bromonitroparaffin with powdered silver.

(f) A closely related synthesis is the electrolysis of salts of aci-nitroparaffins, a reaction which yields substituted dinitroparaffins (352, 419).

$$2R_2C{=}NO_2M \xrightarrow{\text{electrolysis}} R_2C{-}{-}CR_2 + 2M$$
$$\underset{NO_2 \quad NO_2}{\big| \qquad \big|}$$
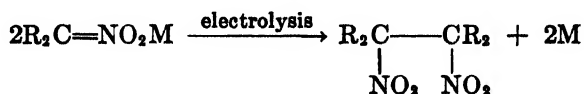
(g) The low-temperature nitration (20–200°C.) of paraffins, either in the liquid phase with nitric acid or in the vapor phase with nitrogen dioxide, yields di- and tri-nitroparaffins. For example, Francis and Young (101) and Poni and Costachescu (303, 304) nitrated isopentane. The latter workers identified 2,3-dinitro-2-methylbutane and 2,3,4-trinitro-2-methylbutane. This reaction is quite general.

(h) Polynitroparaffins can be alkylated in a manner quite analogous to that described in section III for nitroparaffins (89).

(i) Oximes treated with nitrogen tetroxide yield pseudo-nitroles, which can be oxidized to dinitroparaffins having the nitro groups on the same carbon atom (45).

$$R_2C{=}NOH + N_2O_4 \longrightarrow R_2C\underset{NO_2}{\overset{NO}{<}} + HNO_2$$

$$R_2C\underset{NO_2}{\overset{NO}{<}} \xrightarrow{H_2CrO_4} R_2C(NO_2)_2$$
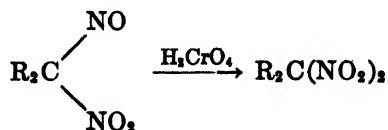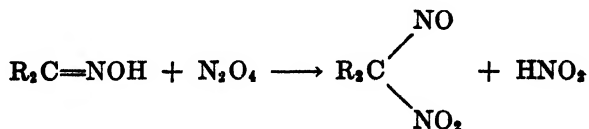
(j) The reaction of concentrated nitric acid upon various organic products to yield polynitro fission products has been discussed in section V. An additional example which seems quite general is the action of nitric acid upon ketones. Thus, ethyl ketones yield 1,1-dinitroethane (66, 98).

(k) Halogen derivatives of polynitro compounds when treated with arsenious oxide lose halogen without suffering reduction of the nitro groups. Duden (89) used this means to obtain dinitromethane from dibromodinitromethane.

(l) The use of the Victor Meyer reaction to yield polynitroparaffins has been mentioned in section II. The production of 1,1-dinitropropane by reaction between the sodium salt of 1-bromo-1-nitropropane and sodium nitrite (375) recalls the Kolbe synthesis.

(m) The addition of a substituted nitroparaffin to a substituted nitroölefin has been reported by Heim (143).

$$C_6H_5CH{=}C(NO_2)C_6H_5 \ + \ C_6H_5CH_2NO_2 \ \longrightarrow \ \underset{\displaystyle C_6H_5CHNO_2}{\overset{\displaystyle C_6H_5CHNO_2}{C_6H_5CH}}$$
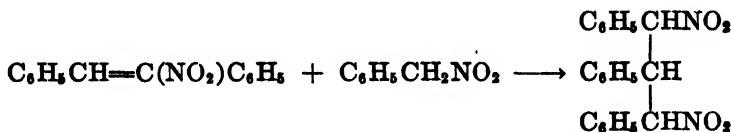
(n) Aryl-substituted nitroölefins are said to form bimolecular reduction products when hydrogenated in the presence of such catalysts as Raney nickel, platinum, and palladium (197, 361, 372).

$$C_6H_5CH{=}CHNO_2 \ + \ H_2 \ \xrightarrow{\text{Pt}} \ \underset{\displaystyle C_6H_5CHCH_2NO_2}{\overset{\displaystyle C_6H_5CHCH_2NO_2}{}}$$
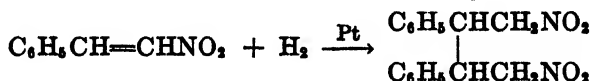
This reaction, however, has been questioned by Heider (142), who believes that the product is a polymer of nitrostyrene.

(o) Holleman (167) treated ω-nitrostyrene in alcohol with aqueous potassium cyanide, then acidified with acetic acid, and obtained a precipitate of a cyano-dinitrodiphenylbutane.

$$O_2NCH_2C(C{\equiv}N)(C_6H_5)CH(C_6H_5)CH_2NO_2$$

VII. Physical Properties of Nitroparaffins

A summary of some of the physical properties of certain nitroparaffins and dinitroparaffins is shown in table 1.

All of the mononitroparaffins are colorless when pure, have dipole moments of approximately 3.2, and boil from 101.7°C. to as high as one wishes to go as the series is ascended. Nitromethane is soluble in water to the extent of 10.5 ml. per 100 ml. of water at 20°C., but this value diminishes sharply as the complexity of the alkyl group increases. The great majority of organic solvents are miscible with nitroparaffins. This includes the aromatic hydrocarbons, alcohols, esters, ketones, ethers, and carboxylic acids. Alkanes, cycloalkanes, and bicycloalkanes are soluble in nitroparaffins with considerable difficulty, and the suggested use of nitromethane (28, 223, 333) in the solvent refining of lubricants is based upon this fact. This miscibility is the basis of Mulliken and Wakeman's classification of hydrocarbons for qualitative organic analysis (280, 281).

The solubility of cellulose esters in nitromethane has been mentioned (section IV, g). One incentive for nitrating isobutane in this laboratory was the ex-

TABLE 1

Physical properties of nitroparaffins

Compound	Melting Point °C.	Boiling Point °C.	Refractive Index	Specific Gravity	References
Nitromethane	−29	101.7	1.3818	1.139 (20°/20°)	(107)
Nitroethane	−90	114	1.3916	1.052 (20°/20)	(107)
1-Nitropropane	−108	132	1.4015	1.003 (20°/20°)	(107)
2-Nitropropane	−93	120	1.3941	0.992 (20°/20°)	(107)
1-Nitrobutane		153	1.4112	0.975 (20°/20°)	(107)
2-Nitrobutane		140	1.4036	0.968 (20°/20°)	(33, 265)
1-Nitro-2-methylpropane		140			(80, 355)
2-Nitro-2-methylpropane	25.5	127			(30, 134)
1-Nitropentane		173	1.4218		(158)
3-Nitropentane		152–154		0.9475 (20°/4°) / 0.9575 (0°/4°)	(33, 35)
1-Nitro-3-methylbutane		164	1.41806	0.9599 (20.6°/4°)	(277)
2-Nitro-2-methylbutane		150	1.4152	0.9783 (0°/4°)	(33, 35, 304)
1-Nitrohexane		193		0.9488 (20°/4°)	(158)
2-Nitrooctane		102–105 at 23 mm.	1.4324 (20°)	0.9224 (20°/20°)	(357)
Trinitromethane	15	45–47 at 22 mm.			(27, 125)
Tetranitromethane	13	126		1.650 (13°/4°)	(27, 343)
1,1-Dinitroethane		185–186		1.3503 (23.5°/23.5°)	(375, 405)
1,2-Dinitroethane		94–96 at 5 mm.	1.4488 (20°)	1.4597 (20°/4°)	(173)
1,1,1-Trinitroethane	56				(125)
Hexanitroethane	142				(408)
2,2-Dinitropropane	54	185.5			(265)
1,4-Dinitrobutane	93	176–178 at 13 mm.			(303)
1,3-Dinitro-2,2-dimethylpropane		140 at 15 mm.			(48)
2,3-Dinitro-2,3-dimethylbutane	210–212				(78, 349)

pectation that 2-methyl-2-nitropropane would be of value as a solvent for cellulose nitrate.   It proved to have a dilution ratio[5] for toluene of only 0.5.   Mixtures of nitroparaffins and alcohols, however, show favorable dilution ratios not only for cellulose nitrate but also for cellulose acetate, vinylite resins, cellulose ethers (225), and the newer mixed esters of cellulose, such as the acetate butyrate and acetate propionate.   For example, a mixture of 75 per cent of 1-butanol (by volume) and 25 per cent of 2-methyl-2-nitropropane shows a value of 2.9 with toluene measured with 1/2 sec. cellulose nitrate (133).   Results with petroleum diluents are somewhat less favorable.

Nitromethane is the only mononitroparaffin which can be detonated with a cap (133), but the homologous mononitroparaffins may explode when heated in a closed container under pressure (238).   The polynitroparaffins are more nearly in oxygen balance and hence explode more easily.   The salts of aci-nitroparaffins detonate much more easily than the parent compounds, and suitable precautions should be taken when these compounds are employed.

The dinitroparaffins are colorless; most of them are crystalline solids which are insoluble in water and have only limited solubility in alkanes but are soluble in most other organic solvents.

The structure of tetranitromethane has been the subject of some controversy, since one of the nitro groups is readily removed by the action of alkali:

$$\cdot \ C(NO_2)_4 + 2KOH \rightarrow KNO_3 + (O_2N)_2C\!\!=\!\!NO_2K + H_2O$$

This reaction does not prove that one of the nitro groups in tetranitromethane is different from the other nitro groups in tetranitromethane but does show that all of the nitro groups in tetranitromethane are different from all of the nitro groups in trinitromethane.   The substitution of a hydrogen atom for a nitro group would be expected to decrease the lability of other groups attached to the same carbon atom.   The symmetry of tetranitromethane has been demonstrated by the fact that its solution in carbon tetrachloride shows a zero dipole moment (399).

VIII. TOXICITY OF NITROPARAFFINS

The nitro group is often present in compounds of high toxicity.   Gibbs and Reichert (113), however, reported that nitromethane, when injected into a dog, exhibited less toxicity than 1-butanol.   Tests made by Henry F. Smyth, Jr.,[6] upon white rats and guinea pigs, using a sample of nitrated propane, led to the conclusion that "the vapors are considerably less toxic than . . . benzene, aniline, carbon disulfide, carbon tetrachloride or nitrobenzene . . .".

Tests made by Willard Machle[7] led to the conclusion that "the nitroparaffins were found to be of about the same order of toxicity as petroleum naphtha.

---

[5] Dilution ratio is the volume of toluene, or other diluent, per unit volume of solvent which just precipitates cellulose nitrate under standard conditions.   High dilution ratio is nearly synonymous with high solvent power.

[6] Laboratory of Hygiene, Philadelphia, Pennsylvania.

[7] College of Medicine, University of Cincinnati, Cincinnati, Ohio.

From the point of view of vapor pressure, they would appear to be somewhat more safe to handle than heptane and somewhat more likely to give rise to significant exposure than n-octane".

IX. Uses of Nitroparaffins

This topic has been discussed recently by Gabriel (107). The solvent powers of nitroparaffins for a great variety of organic compounds, including synthetic resins and lubricating-oil fractions, have been discussed in section VII. The proposed use of nitroparaffins as anti-detonating agents in Diesel fuels (232) has not been confirmed, although tests have been made in several laboratories.

At least for the present, the most important uses of the nitroparaffins depend upon their functioning as chemical intermediates. It is appropriate, therefore, that their chemical reactions should now be considered.

X. Reactions of Nitroparaffins

A. REDUCTION

1. Reduction to amines

This topic has recently been reviewed and extended by Johnson and Degering in this laboratory (178, 179, 180). Successful reductions of aliphatic nitro compounds have been reported with such diverse reagents as tin and hydrochloric acid (156), vanadium sulfate (20), zinc and sulfuric acid (33, 37), zinc and hydrochloric acid (37), zinc and acetic acid (2), lead and acetic acid (318), iron and acetic acid (271), concentrated aqueous sodium hydrosulfite at its boiling point (5), iron and hydrochloric acid (213, 235), the Adams catalyst and hydrogen (339), sodium amalgam (261, 301), aluminum amalgam (274, 277, 350, 369, 381), in vapor phase by hydrogen catalyzed by nickel or copper (337), hydrogen and platinum in various forms (mainly for aromatic nitro compounds) (338), and hydrogen and a palladium catalyst (in the liquid phase) (100, 194, 311). Electrolytic reductions have been reported by Johnson (177), Rakshit (319), who reduced tetranitromethane electrolytically to guanidine, by Pierron (299, 300), and by Chilesotti (70, 71).

Johnson (178) concluded that "the use of reducing agents other than iron and hydrochloric acid gave less favorable results in the reduction of nitroparaffins".

Johnson and Degering also obtained excellent reductions to amines by the use of hydrogen catalyzed by Raney nickel in a Parr rocking bomb. The amines produced by this hydrogenation are, of course, basic and, as is shown in section X, F, such compounds react with primary and secondary nitroparaffins slowly at room temperature, and more vigorously upon heating, to yield complex derivatives such as isoxazoles. In order to obtain good yields of amines it is therefore important to use a vigorous reducing agent, to agitate thoroughly in case the reaction mixture is heterogeneous, and to keep the temperature fairly low.

The reduction of nitroalcohols and nitroglycols is most successful with Raney nickel and hydrogen (136, 137, 138, 139, 140, 179, 386, 390). The nitroalcohols are formed from nitroparaffins and aldehydes (see section X, E) by condensation in the presence of basic catalysts. The nitroalcohols are instable in the pres-

ence of bases because of a reversal of the reaction which produces them. Owing to this instability the yields of aminoalcohols, while often excellent, are sometimes indifferent or even poor. Thus Demuth and Meyer (82) obtained an impure product when sodium amalgam was used. Henry (156) and Tordoir (381) used tin and hydrochloric acid but reported low yields. Mousset (277), Stiénon (369), Tordoir (381), and Montmollin and Achermann (274) used aluminum amalgam and obtained yields of approximately 50 per cent. Buffering the solution with carbon dioxide is usually helpful in such instances.

2. Reduction to alkylhydroxylamines

Alkylhydroxylamines may be isolated from the reaction mixture obtained when nitro compounds are treated with almost any of the usual reducing agents. Often it is possible to control the reduction in such a way as to cause the alkylhydroxylamine to become the main product.

Metallic agents of various kinds may serve to accomplish this reduction. In 1877 Züblin (420) recorded that the reduction of 1-nitrobutane with tin and hydrochloric acid yields a product which acts on Fehling's solution to produce cuprous oxide. Later Meyer and Hoffman (262) reported the synthesis of methylhydroxylamine, CH_3NHOH, by the reduction of nitromethane with tin and hydrochloric acid. Three years later, after showing that boiling with zinc dust and water converted nitrobenzene to phenylhydroxylamine, Bamberger (13) tried the same agents on nitromethane and produced methylhydroxylamine without recognizable quantities of methylamine or ammonia. This result was later confirmed by Beckmann (23) and also by Scheiber (341), who used zinc dust, water, and ammonium chloride to cause the same change.

Similarly, Kirpal (192) prepared alkylhydroxylamines by the action of stannous chloride on nitromethane, nitroethane, "nitropropane", "nitropentane"[8], and 3-nitropropene. Chloropicrin and 1-bromo-1-nitroethane, under like treatment, yield substances which are oxidized by Fehling's solution and which contain halogen.

For the reduction of 2-methyl-1-nitropropene (nitroisobutylene) Bouveault and Wahl (52) employed either aluminum amalgam in ether or zinc powder and acetic acid in ether. Isobutyraldoxime is the main product of this reaction, but there is evidence for the presence of the intermediate unsaturated hydroxylamine, $(CH_3)_2C=CHNHOH$. A similar method serves to convert the esters of nitro acids to the corresponding hydroxylaminic acid esters (49). Charlton and Kenner (67) reduced 2-nitro-2-hydroxymethyl-1,4-butanediol with sodium amalgam and obtained a product which was believed to be $(HOCH_2)_2C(NHOH)-CH_2CH_2OH$, but it was not isolated. Reduction by the use of sodium amalgam was also carried out with a number of other nitroalcohols and nitroglycols.

Duden, Bock, and Reid (90) prepared the 2-piperidyl derivative of 1,1-dinitroethane and reduced it with stannous chloride. Under this treatment the compound lost a nitro group and yielded an oily product, probably the hydroxylamine $C_5H_{10}=NCH_2CH_2NHOH$.

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[8] The article does not state which isomers were employed.

Catalytic hydrogenation is also a useful way in which to prepare hydroxylamine derivatives from nitro compounds. Traube and Schulz (382) preferred this method; they used a catalyst of palladinized barium sulfate and reduced nitromethane and also nitroalcohols catalytically, producing methylhydroxylamine and the hydroxylaminic alcohols. Schmidt, Ascherl, and Mayer (345), who desired to prepare the alkylhydroxylamines without simultaneously producing amines, carried out catalytic reduction with the same catalyst, but employed an aqueous or alcoholic oxalic acid solution as a medium. Alkylhydroxylamines are converted to their oxalates in this solution, and the formation of amines is thus largely prevented. Addition of acetic acid is desirable in some cases.

Electrolytic reduction of nitroparaffins has been reported by Pierron (300), who was able to reduce nitromethane, nitroethane, and 1-nitropropane by the electrolysis of a 10–15 per cent alcoholic solution of the nitroparaffin containing a little sulfuric acid. Satisfactory results were obtained using a nickel cathode in contact with the solution, and a platinum anode separated from it by a porous pot containing sulfuric acid. A cathodic current density of 0.4–0.75 amperes per square decimeter at a temperature not exceeding 15-20°C. gave 65 to 80 per cent of the theoretically available amount of alkylhydroxylamine. At 70°C. comparable yields of amine result. If concentrated sulfuric or hydrochloric acid is used, the products are aldehyde and hydroxylamine. Chilesotti (71) carried out a similar reduction in the presence of small amounts of copper, iron, or tin salts in a process similar to that described in German patents issued to C. F. Boehringer and Sons (43, 44) and in the Johnson patent (177), but since these processes were designed primarily for making aniline and similar compounds his examples were mainly from the aromatic series.

Bruckner, Krámli, and Vinkler (58) carried out electrolytic reductions of nitroparaffins in mixtures of glacial acetic acid, ethanol, and concentrated hydrochloric acid at lead and copper cathodes and reported good yields of both amines and hydroxylamines.

The Dominion Rubber Co., Ltd., and U. S. Rubber Products Co. have studied saturated and unsaturated carbocyclic and heterocyclic hydroxylamines. Presumably, these compounds are of possible value as preservatives for rubber. H. H. Bassford, Jr., recently received a patent on a process for the production of such compounds by reducing the nitro compound in the presence of a non-acidic aqueous solution substantially saturated with the desired cyclic hydroxylamine (22).

Several variations of another general method for converting nitroparaffins to alkylated hydroxylamines have been based on the use of metallic alkyls or of alkyl metallic halides. Dialkylzincs, alkylzinc iodides, and alkylmagnesium iodides have been investigated. Alkyl nitrites and nitroparaffins react with such agents to yield nitroparaffins of higher molecular weight and alkylated reduction products. Thus, nitromethane, when treated with diethylzinc, may yield, among other products, ethylpropylhydroxylamine. The net result of this treatment is, therefore, alkylation on a carbon atom, alkylation on the nitrogen atom, and reduction. The mechanism of this reaction has been variously interpreted.

Bevad (39) found the more available and less flammable alkyl metallic halides preferable to dialkylzinc, in convenience, but they gave less satisfactory yields from nitro compounds.   He postulated the following mechanism (39) for the reaction of the alkylzinc iodide with nitro compounds or alkyl nitrites:

$$\underset{}{R-O-N=O} + R'ZnI \longrightarrow \underset{\underset{ZnI}{\diagup}\;\overset{\overset{OZnI}{|}}{N}\underset{\diagdown\,R'}{}\!\!-R'}{R-O} \longrightarrow R'NOH + ROH$$
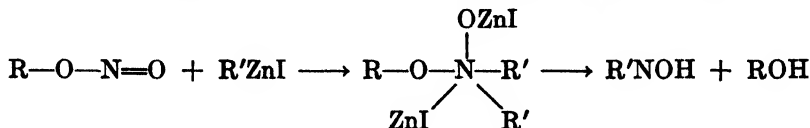
The intermediate addition product yields the dialkylhydroxylamine in which the radicals correspond to those of the alkylzinc halide used.   Alkylmagnesium halides react in exactly the same way with nitrites, but with nitro compounds the reaction is different:

$$RCH_2NO_2 \rightarrow RCH{=}\overset{\overset{O}{\uparrow}}{N}-OH \xrightarrow{R'MgI} \underset{\underset{OMgI}{|}}{R\overset{\overset{R'\;\;MgI\;\;OMgI}{|\;\;\;|\;\;\;}}{\overset{}{C}H-N-R'}} \longrightarrow R\overset{\overset{R'\;R'}{|\;\;}}{C}H\overset{}{N}OH$$

$$\xrightarrow{R'MgI} \underset{\underset{MgI\;\;R'\;\;OMgI}{|\;\;\;\;|\;\;\diagdown}}{RCH{-}\overset{\overset{OMgI}{|}}{N}R'} \longrightarrow \underset{\underset{R'}{|}}{RCH_2NOH} + ROH$$
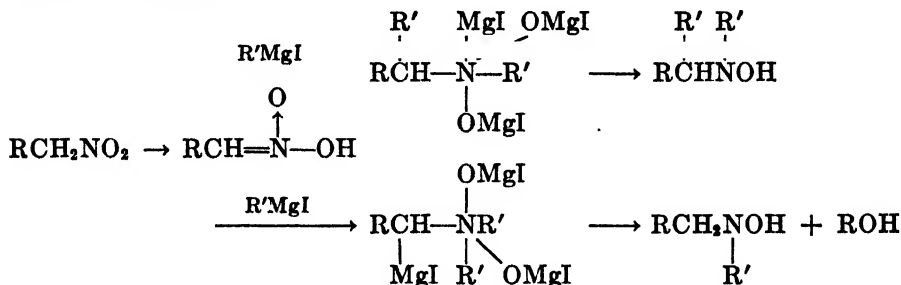
Not all of these products were found by every investigator.   Moureu (276) had stated that diethylhydroxylamine was the only product from the action of ethylmagnesium iodide on nitroethane.   Bevad demonstrated (39) the presence of more complex products, such as ethyl-sec-butylhydroxylamine, $CH_3CH(C_2H_5)$-$N(C_2H_5)OH$.   Ethyl alcohol was found to be present.   Nitroethane and propylmagnesium iodide react similarly, giving (1-methylbutyl)propylhydroxylamine and propylethylhydroxylamine.   Bevad tried many variations of this reaction, most of which appear in table 2.

Wang (397) has interpreted these reactions of alkylmagnesium bromide with

$$CH_2{=}\overset{\overset{O}{\uparrow}}{N}-OMgBr$$

nitroparaffins by postulating the existence of $CH_2{=}N-OMgBr$ as an intermediate in the action of phenylmagnesium bromide on nitromethane.

The variety and diversity of reactions for preparations of the alkylated hydroxylamines may be seen from the summary in table 2.

3. Reduction to oximes

This reaction has been reported by Konovalov (209), by Ponzio (305), by Bamberger and Weiler (19), by von Braun and Sobecki (393), and by Johnson (178, 180).   Johnson and Degering obtained a yield of 43 per cent by the use of zinc dust and glacial acetic acid, using a technic similar to that of Konovalov. The aldehyde was distilled out and estimated by reaction with excess hydroxyl-

amine hydrochloride, followed by titration of the liberated hydrochloric acid (180).

<div style="text-align:center">

TABLE 2

Reduction of nitroparaffins to alkylhydroxylamines

</div>

COMPOUND	REACTANTS	REFER-ENCES
β-Methylhydroxylamine: b.p. 62.5°C. at 15 mm. (193); m.p. 42°C. on rapid heating (193); $d_4^{20^\circ} = 1.003$ (59, 60); $n_D^{20^\circ} = 1.41638$ (60)	Nitromethane and stannous chloride	(164)
	Nitromethane and stannous chloride	(192)
	Catalytic hydrogenation in alcoholic oxalic acid in the presence of palladinized barium sulfate	(345)
	Electrolytic reduction of nitromethane in dilute alcoholic sulfuric acid at 15–20°C.	(300)
Derivatives: hydrochloride, m.p 88–90°C.; hydrobromide, m.p. 73°C.; picrate, m.p. 128–130°C	Nitromethane with zinc dust and water at the boiling point	(13)
	Ammonium chloride and zinc dust in water on nitromethane at 0–15°C.	(23)
β-Ethylhydroxylamine: m.p. 56–60°C. (193); $d_4^{20^\circ} = 0.9079$ (59, 60); $d_0^{20^\circ} = 0.9079$ (59, 60) $n_D^{20^\circ} = 1.41519$ (59, 60)	Electrolytic reduction of nitroethane in dilute alcoholic sulfuric acid at 15–20°C.	(300)
	Stannous chloride on nitroethane	(192)
Oxalate, m.p. 95–97°C.	1,1-Dinitroethane (as piperidyl derivative) with stannous chloride $\rightarrow$ piperidyl derivative, C_5H_{10}=NCH$_2$CH$_2$NHOH	(90)
β,β-Diethylhydroxylamine: b.p. 132–133°C. at 760 mm. (39); 40.5–41°C. at 10 mm. (39); m.p. -10°C. (276); $d_4^{20^\circ} = 0.8670$ (39); $d_0^{0^\circ} = 0.8853$ (39); $n_D^{20^\circ}$ not given	Diphenylnitrosamine and diethylzinc; then water	(216)
	Nitrogen dioxide on ethylmagnesium iodide in cold ether; then water	(404)
	Ethylmagnesium iodide on isoamyl nitrite in ether; then water	(276)
	Ethylmagnesium iodide on nitroethane; then decomposition of product with water	(276)
Hydrochloride, m.p. 63°C. (404)	Ethylmagnesium iodide on nitroethane; then decomposition of product with water	(39)
Hydrobromide (hygroscopic), m.p. 55–56.5°C. (39)	Ethylzinc iodide on isoamyl nitrite in ether; then decomposition of product with water	(39)
Oxalate, m.p. 138°C. (404), 136–137°C. (91)	Diethylzinc and isoamyl nitrite or other alkyl nitrite in ether; then water	(37)
	Diethylzinc in cold ether with a cold ether solution of nitrosyl chloride	(38)
β-Propylhydroxylamine: m.p. about 46°C. (193)	Electrolytic reduction of 1-nitropropane in dilute alcoholic sulfuric acid at 15–20°C.	(300)
	Stannous chloride on 1-nitropropane	(192)
β-Ethyl-β-propylhydroxylamine: b.p. 147–150°C. at atmospheric pressure (39); $d_4^{20^\circ} = 0.8581$, $d_0^{0^\circ} = 0.8735$ (39)	Propylmagnesium iodide on nitroethane	(39)
	Ethylmagnesium iodide on nitropropane	(39)
	Diethylzinc with methylzinc and nitromethane in cold ether	(35, 36)

TABLE 2—*Concluded*

COMPOUND	REACTANTS	REFER-ENCES
Hydrochloride (hygroscopic), m.p. 64–65°C.; hydrobromide (very hygroscopic), m.p. 49–51°C.		
β,β-Dipropylhydroxylamine: b.p. 153–156°C. (91), 156–158°C. at 753 mm. (39), 72–74°C. at 30 mm. (242), 69–70°C. at 17–20 mm. (39); m.p. 27.5–29.5°C. (39)	Propylmagnesium iodide on isopropyl nitrite in ether; then water	(39)
	Dipropylzinc on propyl nitrite in ether; then water	(35, 36)
Hydrochloride (not hygroscopic), m.p. 88–90°C. (39); hydrobromide (slightly hygroscopic), sinters at 70°C. and melts at 74–75°C. (39); acid oxalate, m.p. 139°C. (91)		
β-Isopropylhydroxylamine: m.p. 87°C.; sublimes at 40°C. at 25 mm.		
Hydrochloride melts *ca.* 55°C. (very hygroscopic)		
β,β-Diisopropylhydroxylamine: b.p. 137–142°C. (91)	Isopropylzinc iodide with isoamyl nitrite in cold ether	(39)
Hydrochloride, m.p. 144–145°C. (39)		
β-Ethyl-β-*sec.*-butylhydroxylamine; b.p. 154–157°C., 84–87°C. at 75 mm. (M.W.); 155–158°C. at 756 mm. (39), 57–58°C. at 8 mm. (39); d$_4^{20}$ = 0.892, d$_4^{25}$ = 0.8757 (39) Hydrochloride, m.p. 56–57°C.; neutral oxalate, m.p. 114–115°C.; acid oxalate, m.p. 93–95°C.	Ethylmagnesium iodide on nitroethane in ether; then decomposition of products with water	(39)
	Ethylzinc iodide on nitroethane in ether; then decomposition of products with water	(39)
	Diethylzinc on nitroethane in cold ether; then ice water on the products	(29, 35, 37)
	Diethylzinc on nitroethane in cold ether; then ice water on the products	(215, 216)
	Diethylzinc on nitroethane in ether in the absence of air; ice water after 3 weeks	(242)

There is strong evidence that certain prior workers have confused the reduction of nitroparaffins to oximes with the Nef reaction (see section X, B, 2) by which an aldehyde or ketone is produced by the treatment of a salt of an aci-nitroparaffin with a strong acid. Thus, Markovnikov added alkali salts of

aci-nitroparaffins to stannous chloride and hydrochloric acid and measured his yield by the ketones isolated. This reaction gives excellent yields of ketone even in the absence of any reducing agent. Probably if oximes *per se* are of commercial interest, so that it seems advisable to synthesize them from nitroparaffins, they will be made from aldehydes and/or ketones and the hydroxylamine produced by the action of sulfuric acid upon primary nitroparaffins. Certainly the acidification of salts of aci-nitroparaffins is the practical way of making aldehydes and ketones from nitroparaffins.

An interesting indirect method of converting primary and secondary nitroparaffins to oximes consists in alkylation to nitronic esters, followed by pyrolysis of the latter to oximes and aldehydes.

$$R_2C{=}NO_2Na + CH_3I \longrightarrow R_2C{=}\overset{\overset{O}{\uparrow}}{N}{-}OCH_3 + NaI$$

$$R_2C{=}\overset{\overset{O}{\uparrow}}{N}{-}OCH_3 \xrightarrow{\text{heat}} R_2C{=}NOH + HCHO$$
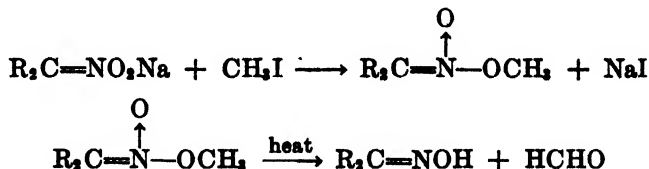
For a discussion of this reaction, the reader is referred to Thurston and Shriner (378).

B. ACTION OF MINERAL ACIDS

1. Action of mineral acids to yield hydroxamic and carboxylic acids

This is one of the first-discovered reactions of the primary nitroparaffins, having been reported by Meyer and Wurster (272) only a year after the announcement of the first nitroalkane. Table 3 summarizes much of the prior art.

This rather remarkable hydrolysis of a CH_2NO_2 group to a carboxyl group and a salt of hydroxylamine has aroused the interest of several investigators, who have proposed various mechanisms, all postulating aci-nitroparaffins and hydroxamic acids as two of the intermediates.

Conclusive evidence for the existence of aci-nitroparaffins ($RCH{=}NO_2H$ and $R_2C{=}NO_2H$) has been derived from a number of sources. They can be obtained by the action of acids upon metallic derivatives of the nitroparaffins. Holleman (166) found that *m*-nitrophenylnitromethane gives a yellow sodium salt and that acidification with an equivalent of hydrochloric acid produces a yellow solution which has a higher conductivity than that of the sodium chloride which it contains. On standing, the color disappears and the conductivity falls to that of the sodium chloride.[9] Hantzsch and Schultze (126) isolated the aci forms of phenylnitromethane and *p*-bromophenylnitromethane by passing a mineral acid into the ice-cold solution of the sodium salt.

The true aliphatic nitro compounds give no color with ferric chloride, while the aci derivatives give a red-brown hue, typical of the enol linkage. The nitro

[9] In Sidgwick's *Organic Chemistry of Nitrogen* (revised by T. W. J. Taylor and W. Baker; Oxford University Press, London (1937)), pp. 228-47, there is an excellent treatment of this topic.

compound is but slightly soluble in water and only slowly soluble in alkali, while the aci derivative is much more soluble in water and instantly soluble in sodium hydroxide solution. The nitro derivative reacts slowly with bromine, while the aci compound adds bromine almost instantaneously. Definite melting points have been obtained for several substituted aci-nitroparaffins.

Maron and La Mer (246) have studied the kinetics of the neutralization of nitromethane, nitroethane, and 2-nitropropane, since these compounds (as well as other primary and secondary nitroparaffins) function as typical pseudo

TABLE 3

Conversion of nitroparaffins to alkanoic acids

NITROPARAFFIN	ACID	PRODUCTS	PRIOR WORK (AUTHORS AND REFERENCES)
$C_2H_5NO_2$	H_2SO_4	CH_3COOH, $(NH_2OH)_2SO_4$	Meyer *et al.* (270)
CH_3NO_2	H_2SO_4	CO, $(NH_2OH)_2SO_4$	Preibisch (313)
CH_3NO_2	H_2SO_4	CO, CO_2, $(NH_2OH)_2SO_4$, $(NH_4)_2SO_4$	Mel'nikov (256)
CH_3NO_2	HCl	$HCOOH$, NH_2OHCl	
$C_2H_5NO_2$	HCl	CH_3COOH, NH_2OHCl	Meyer and Locher (265)
$C_3H_7NO_2$	HCl	C_2H_5COOH, NH_2OHCl	
$C_2H_5NO_2$	H_3PO_4	CH_3COOH, $NH_4H_2PO_4$	Geuther (112)
$C_2H_5NO_2$	H_3PO_4	CH_3COOH, NH_2OH salt	
$C_2H_5NO_2$	H_2SO_4	CH_3COOH, NH_2OH salt	Werner (401)
$C_2H_5NO_2$	HCl	CH_3COOH, NH_2OH salt	
$C_2H_5NO_2$	H_2SO_4	CH_3COOH, NH_2OH salt	
i-$C_3H_7C(NOH)NO_2$	H_2SO_4	$CH_3CH(CH_3)COOH$, N_2O	Demole (80)
$C_4H_9NO_2$	HCl	C_3H_7COOH	Züblin (420)
$O_2N(CH_2)_2CN$	HCl	Succinic acid	Henry (153, 154)
$C_6H_5CH_2NO_2$	HCl	C_6H_5COOH	Gabriel and Koppe (109)
n-$C_5H_{11}CH_2NO_2$	HCl	n-$C_5H_{11}COOH$	
n-$C_6H_{13}CH_2NO_2$	HCl	n-$C_6H_{13}COOH$ + NH_2OH salts	
n-$C_7H_{15}CH_2NO_2$	H_2SO_4 HCl	n-$C_7H_{15}COOH$ + NH_2OH salts	Worstall (414, 418)
n-$C_8H_{17}CH_2NO_2$	HCl	n-$C_8H_{17}COOH$ + NH_2OH salts	

acids. The same authors studied the kinetics of the isomerization of nitroethane from the aci to the nitro form in water and in deuterium oxide. The rate constants were the same in the two media (247). Maron and Shedlovsky (249) obtained the value 4×10^{-5} for the ionization constant of aci-nitroethane at 23°C. This is of the same order of magnitude as the value 7×10^{-5} obtained by Junell from kinetic measurements at 0°C. (184). For an excellent discussion of the nitroparaffins as pseudo acids, see Maron and La Mer (248).

When the salts of nitroparaffins are warmed with concentrated acid they decompose into fatty acids and salts of hydroxylamine, although the action of dilute acid yields aldehyde or ketone (see section X, B, 3) while acids as feeble

as carbonic acid regenerate the nitroparaffin. The nitronic acids[10] may therefore be considered as intermediates in the conversion of parimary nitroparaffins to carboxylic acids.

This mechanism implies that the tautomerization of nitroparaffins to the aci derivatives is either spontaneous or is accelerated by acids. That the latter is true was demonstrated by Lowry and Magson (234), who found that nitrocamphor reaches tautomeric equilibrium between the aci and the nitro forms to the extent of 99.5 per cent in 33 min. in the presence of $N/10$ trichloracetic acid dissolved in chloroform, although a period of six years was required in the absence of a catalyst.

Bamberger and Rust (17) suggested that the hydroxamic acids should also be considered to function as intermediates in this reaction. They obtained a 2 per cent yield of the hydroxamic acid from phenylnitromethane. By manipulating the conditions Lippincott and Hass (229) were able to obtain a 44 per cent yield of propionohydroxamic acid from 1-nitropropane. Since yields of carboxylic acids in excess of 90 per cent were obtained (229), it is evident that under these conditions at least a large proportion of the hydrolysis proceeds through the hydroxamic acids.

The mechanism by which the aci-nitroparaffin is converted to the hydroxamic acid is still undecided, but the fact that fairly concentrated sulfuric acid gives the best rates and yields is at least suggestive. The carbon–nitrogen double bond of the aci-nitroparaffin would be expected to add sulfuric acid rapidly only if the latter were not too dilute.

$$\text{RCH}{=}\text{NO}_2\text{H} \;+\; \text{H}_2\text{SO}_4 \;\longrightarrow\; \underset{\underset{\text{HSO}_4\;\;\text{H}}{|\quad\;\;|}}{\text{RCH}{-}\overset{\overset{\text{O}}{\uparrow}}{\text{N}}\text{OH}}$$
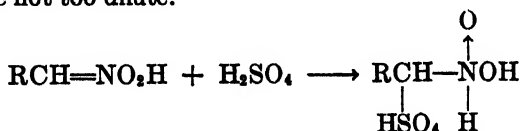
This product, having a hydrogen and hydroxyl attached to the same nitrogen atom, would be expected to lose water and form a nitroso derivative:

$$\underset{\underset{\text{HSO}_4\;\;\text{H}}{|\quad\;\;|}}{\text{RCH}{-}\overset{\overset{\text{O}}{\uparrow}}{\text{N}}{-}\text{OH}} \;\longrightarrow\; \underset{\underset{\text{HSO}_4}{|}}{\text{RCH}{-}\text{N}{=}\text{O}}$$
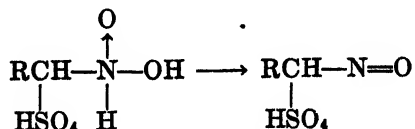
which would rearrange to the mixed anhydride of sulfuric acid and a hydroxamic acid,

$$\underset{\underset{\text{HSO}_4}{|}}{\text{RCH}{-}\text{N}{=}\text{O}} \;\longrightarrow\; \underset{\underset{\text{HSO}_4}{|}}{\text{RC}{=}\text{NOH}}$$
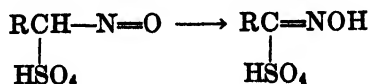
just as other nitroso compounds invariably do if a hydrogen atom is available on the carbon atom holding the nitroso group.

[10] The term "nitronic acid" is synonymous with "aci-nitro derivative" and should not be confused with nitrolic acid, $\text{RC(NO}_2\text{)}{=}\text{NOH}$.

This last compound would be hydrolyzed to the hydroxamic acid, which would undergo further hydrolysis to yield the carboxylic acid and hydroxylamine acid sulfate:

$$RC{=}NOH + H_2O \longrightarrow RC{=}NOH + H_2SO_4$$
$$\underset{HSO_4}{\mid} \qquad\qquad\qquad \underset{OH}{\mid}$$

$$RC{=}NOH + H_2O + H_2SO_4 \longrightarrow RCOOH + NH_3OH{\cdot}HSO_4{}^{[11]}$$
$$\underset{OH}{\mid}$$

$$\updownarrow$$

$$RC\overset{\displaystyle O}{\underset{\displaystyle NHOH}{\diagup\!\!\diagdown}}$$
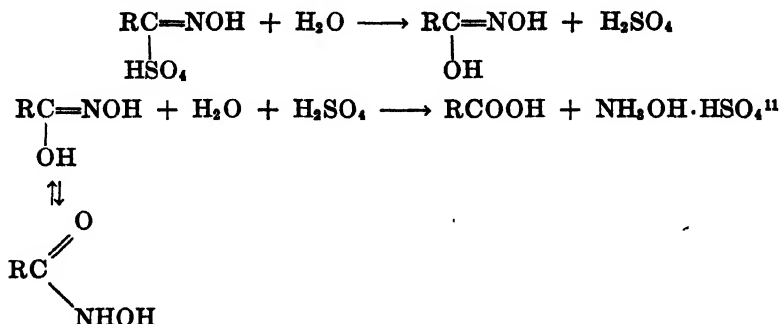
In order to increase the yield of hydroxamic acid to nearly 50 per cent it is only necessary to use anhydrous sulfuric acid at 60°C., pour the product over crushed ice, and neutralize the acid with calcium carbonate (229). This result may prove to be of more than academic interest (227), since C. C. Dewitt has discovered that the hydroxamic acids are successful as flotation agents for certain copper ores (85).

For more than a year this reaction has served as the commercial source of the hydroxylammonium salts produced in the United States. It has interesting possibilities for the manufacture of the propionic and butyric acids now used in the manufacture of cellulose esters, which can thus be produced from the hydrocarbons of natural gas by a two-step synthesis.

An application of this reaction has been suggested by Ellis (95), who disclosed the synthesis of mandelic acid (a widely used urinary antiseptic) by the following reactions:

$$C_6H_5CHO + CH_3NO_2 \rightarrow C_6H_5CHOHCH_2NO_2$$

$$C_6H_5CHOHCH_2NO_2 + HCl + H_2O \rightarrow C_6H_5CHOHCOOH + NH_3OHCl$$
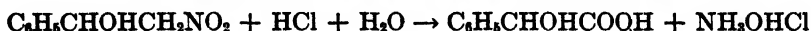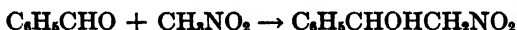
Rosenmund (334), however, reported that 1-phenyl-2-nitroethanol yields ω-nitrostyrene when treated with mineral acids.

2. Action of mineral acids upon salts of aci-nitroparaffins

In the foregoing discussion brief mention has been made of the reaction discovered by Nef (284) by which acidification of the salts of aci-nitroparaffins by strong mineral acids yields aldehydes or ketones.

$$2RCH{=}NO_2Na + 2H_2SO_4 \rightarrow 2RCHO + 2NaHSO_4 + N_2O + H_2O$$

$$2R_2C{=}NO_2Na + 2H_2SO_4 \rightarrow 2R_2CO + 2NaHSO_4 + N_2O + H_2O$$

This reaction has recently been reviewed and extended by Johnson and Degering in this laboratory (178), who found that the calcium salts react as

---

[11] This is essentially the mechanism proposed by Nenitzescu and Isăcescu (286).

readily as the sodium derivatives. Except for 2-methyl-1-nitropropane, which gave a yield of 32.4 per cent and a conversion of 27.5 per cent, all of the nitroparaffins investigated gave conversions of 80 to 85 per cent. These included nitroethane, 1-nitropropane, 2-nitropropane, 1-nitrobutane, and 2-nitrobutane. The following general directions are given: "One-sixth of a mole of nitroparaffin dissolved in 150 ml. of a solution containing 8 g. of NaOH was added dropwise to an ice-cold mixture of 25 ml. concentrated sulfuric acid in 160 ml. of water. Efficient agitation was used during the addition." The aldehyde or ketone was removed by distillation.

3. The red-white-and-blue reaction

The action of nitrous acid upon nitroparaffins is interesting because of its suitability for distinguishing between primary, secondary, and tertiary derivatives.

$$RCH_2NO_2 + HONO \longrightarrow \begin{bmatrix} NO \\ | \\ RCHNO_2 \end{bmatrix} \longrightarrow RC \overset{\displaystyle \nearrow NOH}{\underset{\displaystyle \searrow NO_2}{}}$$

Nitrolic acid
(salts are red)

$$R_2CHNO_2 + HONO \longrightarrow R_2C \overset{\displaystyle \nearrow NO}{\underset{\displaystyle \searrow NO_2}{}}$$

Pseudo-nitrole (blue)

$$R_3CNO_2 + HONO \longrightarrow \text{No reaction (white)}$$
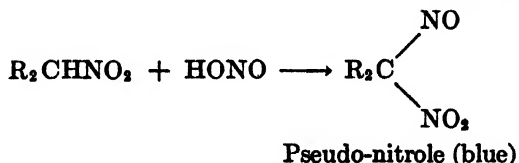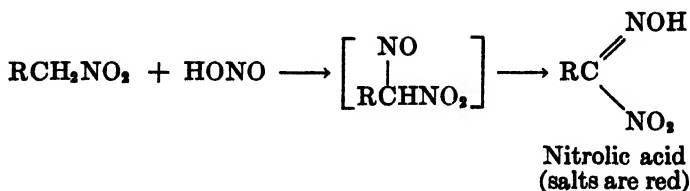
The salts of the nitrolic acids are bright red even in solution and explosive when dry. With acids they yield polymers of nitrile oxides, $R—C\equiv N\rightarrow O$. They are decomposed to carboxylic acids by the action of sulfuric acid (80, 257).

$$CH_3\underset{\displaystyle |}{CH}C\overset{\displaystyle \nearrow NOH}{\underset{\displaystyle \searrow NO_2}{}} \xrightarrow{H_2SO_4} CH_3\underset{\displaystyle |}{CH}COOH + N_2O$$
$$\overset{CH_3}{} \qquad\qquad\qquad \overset{CH_3}{}$$
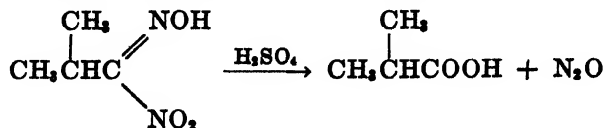
The pseudo-nitroles show behavior typical of nitroso compounds; they are blue in solution but the crystalline forms are usually colorless because of dimerization. Their structure has been established by a modification of the Victor Meyer reaction (302).

$$(CH_3)_2C\overset{\displaystyle \nearrow Br}{\underset{\displaystyle \searrow NO}{}} + AgNO_2 \longrightarrow (CH_3)_2C\overset{\displaystyle \nearrow NO_2}{\underset{\displaystyle \searrow NO}{}} + AgBr$$
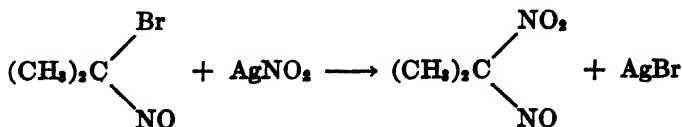
Although only historical importance can now be attached to the method of classifying alcohols as primary, secondary, or tertiary by conversion to the iodide and thence to the nitro derivative which is treated with nitrous acid, the last step is still of value in research with aliphatic nitro compounds involving proofs of structure.

C. ACTION OF BASES UPON NITROPARAFFINS

The behavior of primary and secondary nitroparaffins as pseudo acids has been referred to in section X, B, 1. There is one aspect of this phenomenon which has aroused keen controversy and is still unsettled. Kuhn and Albrecht (214) showed that when the sodium salt of optically active 2-nitrobutane was prepared by reaction between aqueous sodium hydroxide and the nitroparaffin dissolved in methanol the optical activity disappeared completely. When sodium methoxide dissolved in methanol was employed, the activity remained.

Shriner and Young (357) confirmed these results, using 2-nitroöctane and sodium ethoxide. They also regenerated the nitroparaffin by treatment with alcoholic hydrogen chloride at $-70°C.$ and found 71 per cent of the original rotation.

The formula for an aci-nitroparaffin originally proposed by Nef was

$$\begin{array}{cc} R & O \\ | & \| \\ R-C=N-OH \end{array}$$
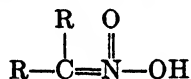
which in modern notation would be written:

$$\begin{array}{cc} R & O \\ & \uparrow \\ R-C=N-OH \end{array}$$
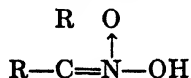
A compound having this structure would yield a salt possessing a plane of symmetry and hence optically inactive. The formation of this structure thus accounts for the observed racemization. Kuhn and Albrecht (214), Shriner and Young (357), and Hurd (115), after considering and rejecting a ring system, all favor for the optically active salt a formula which may be written electronically as

$$\begin{array}{ccc} R' & :O: & \\ R:\overset{..}{C}:N+ & & Na^+ \\ & O: & \end{array}$$

or as follows:

$$\begin{array}{ccc} R' & O^- & \\ | & \nearrow & \\ R-C-N+ & & Na^+ \\ & \diagdown\!\diagdown & \\ & O & \end{array}$$
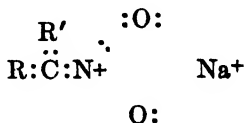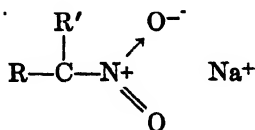
Sidgwick, Taylor, and Baker[12] have objected to this formulation and have suggested (tentatively) that the "sodium salts" formed by the action of sodium alkoxides are really produced by the addition of this reagent to the nitro group.

$$
\begin{array}{ccc}
\underset{\underset{H}{|}}{\overset{\overset{R'}{|}}{R-C-N}}\nearrow^{O}_{\diagdown\diagdown O} + RONa & \longrightarrow & \underset{\underset{H}{|}\ \underset{OR}{|}}{\overset{\overset{R'}{|}\ \overset{O}{\nearrow}}{R-C-N-O-Na}}
\end{array}
$$
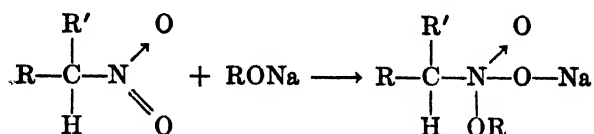
This reaction would, of course, not destroy the asymmetry of the molecule. Meisenheimer (251) has shown that potassium methoxide adds to 2-nitronaphthalene. Shriner, Adams, and Marvel (114) report, however, that 2-methyl-2-nitropropane does not add sodium ethoxide. Since this tertiary nitroparaffin is much more closely related to the compounds in question than is 2-nitronaphthalene, it must be admitted that at present the weight of the evidence favors the formulation of Kuhn and Albrecht. The recent work of Ray and Palinchak (324) proves that the matter is still being actively investigated.

Nitromethane, compared to other nitroparaffins, is uniquely sensitive to the action of alkali. Sodium or potassium hydroxide converts it to salts of methazonic acid by a reaction in which two molecules (106, 222) condense with loss of water. This may be interpreted as an addition of nitromethane to the carbon–nitrogen double bond of the potassium salt, followed by rearrangement and

$$
\underset{NO_2K}{\overset{CH_2}{\|}} + \underset{H}{\overset{CH_2NO_2}{|}} \longrightarrow \underset{\underset{\underset{H\quad K}{O\quad O}}{\diagup\diagdown}}{\overset{CH_2CH_2NO_2}{\underset{N}{|}}} \longrightarrow \underset{NOH}{\overset{CHCH=NO_2K}{\|}} + H_2O
$$
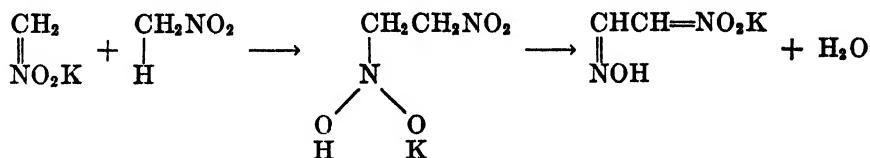
loss of water. Upon further treatment with strong alkali, methazonic acid is converted to nitroacetic acid (364).

$$
HON=CHCH=NO_2K \xrightarrow{-H_2O} N\equiv CCH=NO_2K \xrightarrow[+H_2O]{+KOH}
$$

$$
KOOCCH=NO_2K \xrightarrow{H^+} HOOCCH_2NO_2
$$
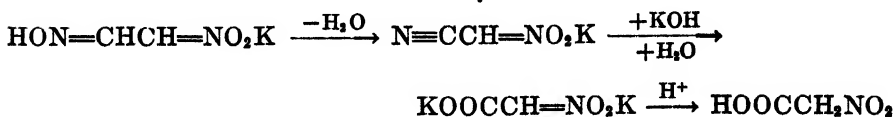
The crystalline sodium salt of nitroacetic acid can be obtained directly in a single operation by dropping nitromethane into a 50 per cent aqueous solution of sodium hydroxide maintained at 50°C., heating the solution to boiling for 10 min., and cooling. The free acid is obtained by acidification with hydrogen chloride of the finely divided salt suspended in ether.

When the sodium salt of aci-nitromethane is treated with mercuric chloride,.

[12] See *The Organic Chemistry of Nitrogen*, by N. V. Sidgwick, revised by T. W. J. Taylor and W. Baker. Oxford University Press, London (1937).

a white precipitate is formed which is probably the mercuric salt of aci-nitromethane. This quickly loses water, forming mercuric fulminate (266, 284).

$$2CH_2{=}NO_2Na + HgCl_2 \longrightarrow (CH_2{=}NO_2)_2Hg \xrightarrow{2H_2O} Hg(ONC)_2$$
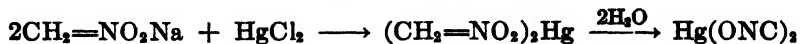
The homologous nitroparaffins yield trialkylisoxazoles upon reaction with alkali. This reaction has recently been studied by Lippincott (228) in the research laboratory of the Commercial Solvents Corporation. The following reactions are postulated:

$$RCH_2NO_2 \rightleftarrows RCH{=}NO_2H$$
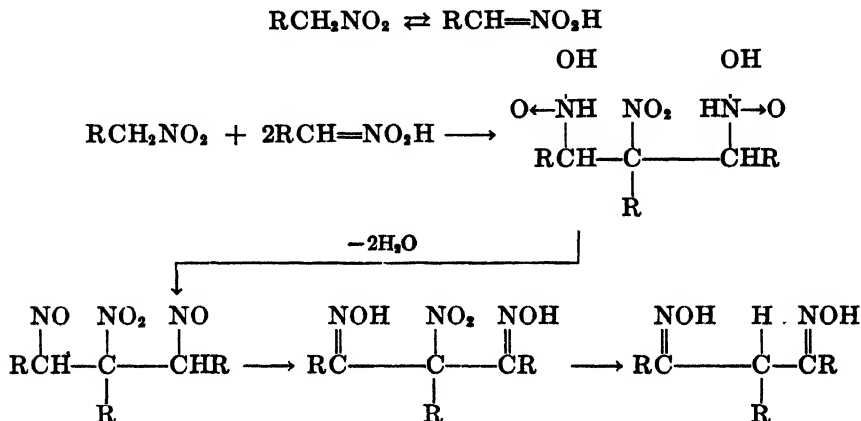
This last step is the reversal of an ordinary nitration reaction and recalls the conversion of tetranitromethane to trinitromethane by the action of bases. In both cases a carbon atom heavily loaded with negative substituents loses a nitro group in an alkaline environment. One of the distinctive features of Lippincott's work is that, by the use of anhydrous organic amines instead of the inorganic bases employed by previous workers, the dioximes—long suspected as intermediates in this reaction—were actually isolated in fair yield.
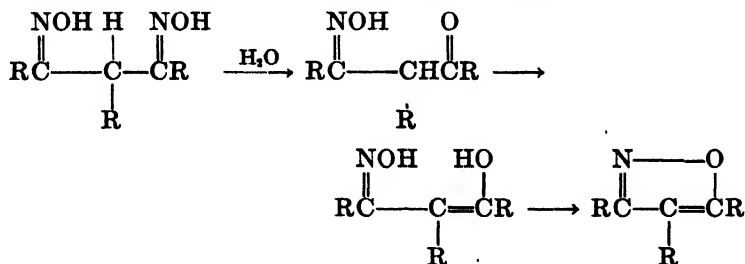
D. HALOGENATION

1. Halogenation in the presence of bases

Aliphatic fluoronitro compounds have not so far been reported.

The first chlorination of a nitroparaffin was reported by Preibisch (314), who treated nitromethane with bleaching powder and reported that he obtained

monochloronitromethane. Tscherniak (383), on repeating the work, obtained only chloropicrin and unchanged nitromethane. Since Preibisch gave a boiling point (98°C.) which is correct for the nitromethane–chloropicrin azeotrope and is incorrect for monochloronitromethane (b.p. 122–123°C.), it is evident that he was in error. Tscherniak obtained the monochloro derivative by converting nitromethane to the sodium salt, washing and drying the salt, and adding it in small portions to saturated chlorine water.

Dichloronitromethane, while not obtained by the chlorination of methane (probably because of instability in the presence of bases), was produced in poor yield by Strickland (370) by nitrating dichloromethane in the vapor phase.

A process for the conversion of nitromethane to chloropicrin was devised by Ramage (321). The chlorination is carried out in the presence of an aqueous suspension of calcium carbonate, which ensures the maintenance of faintly acidic conditions; almost quantitative yields are said to result. Vanderbilt (388) obtained similar results using an alkali or alkaline-earth hypochlorite. In both of these processes the avoidance of the prolonged action of a strong base upon nitromethane and its chlorinated derivatives is an essential feature. In view of the sensitivity of nitroparaffins to the action of alkali, this is easily understood.

Since chloropicrin has recently been comprehensively reviewed (175), little need be added here. It should be mentioned, however, that its value as a toxic vapor for military purposes seems to have been terminated by the use of efficient active carbons, which remove it completely from the air breathed by the wearer of a modern respirator. Chloropicrin is, however, finding increasing use as a fumigant and insecticide and seems to have an important future as a soil-sterilizing agent. Yields of pineapples have been increased 200 per cent by treating heavily infested soils with chloropicrin.

L. Henry (152) produced the monochloro derivatives of nitroethane, 1-nitro-propane, and 2-nitropropane by bubbling gaseous chlorine into an aqueous solution of the sodium salt of the aci-nitroparaffin. Shaw (356) similarly prepared 1-chloro-1-nitro-2-methylpropane. Several other chloronitroparaffins have been obtained by means other than the chlorination of nitroparaffins. These methods include the following: (1) the nitration of chloroparaffins (212, 273) or of epichlorohydrin (9) or the nitration of chloroaromatic compounds such as naphthalene tetrachloride with fuming nitric acid (323); (2) the addition of chlorine to nitroölefins (372); (3) the action of nitrogen tetroxide on chloro-olefins (7, 8, 41, 161, 201); (4) the action of nitrosyl chloride or hypochlorites on oximes (42, 307, 330, 331); (5) the action of aqua regia upon all sorts of organic materials (320); (6) the action of phosphorus pentachloride on nitroalcohols (since chlorinated aldehydes may be used to prepare the nitroalcohols, poly-chloronitroparaffins are easily obtained by this method) (152, 297, 355, 356); (7) the action of hypochlorites upon such nitro compounds as picric acid (224); (8) the action of silver nitrite on chloroiodoparaffins (148, 149, 150, 152, 296); (9) direct chlorination of trinitromethane, yielding chlorotrinitromethane in nitric acid solution (239); (10) the chlorination of mercuric fulminate, which yields chloropicrin (190).

Although Henry gave directions for avoiding the formation of dichloronitro-paraffins in his chlorinations, and Losanitsch (233) had dichlorinated dinitro-methane, the conversion of either a mononitroparaffin or a monochloronitro-paraffin to a dichloronitroparaffin was not reported until 1937. Strickland (370) found that, with the exception of monochloronitromethane, the conversion of the monochloride to the dichloride proceeds as smoothly as the production of the monochloro derivative. The dichlorination can also be performed in a· single operation, using 2 moles of base and chlorine to 1 mole of nitroparaffin (54). Calcium salts may be employed. Strickland made the following compounds not previously reported: 1-chloro-1-nitrobutane, 1,1-dichloro-1-nitro-ethane, 1,1-dichloro-1-nitropropane, 1,1-dichloro-1-nitrobutane, and 1,1-dichloro-1-nitro-2-methylpropane.

Because of the low cost of the raw materials and the ease of their preparation, the chloronitroparaffins are of interest as readily available, relatively inexpensive compounds. 1,1-Dichloro-1-nitroethane gives promise as an insecticide. It is effective against many insects and when pure it is free from the intense lachry-mal property of chloropicrin. The commercial material contains a little chlo-ropicrin, which serves as a warning agent. Campbell (63) has reported that chloronitroparaffins are powerful inhibitors of gelling in ultra-accelerated rubber cements. Hixon and Miller (160) have disclosed the use of chloronitroparaffins as selective solvents in the refining of lubricants.

The bromination of nitroparaffins has been extensively studied. Reaction between bromine and an aci-nitroparaffin or a salt of an aci-nitroparaffin is so nearly instantaneous that it has been used as a means for measuring the change of a nitroparaffin to the tautomeric nitronic acid (182–185). Most of the possible bromo-substitution products of the simple nitroparaffins in which the bro-mine atom or atoms and the nitro group are on the same carbon atom have been reported. They are extremely easy to make but are, at least for most purposes, incapable of competing economically with their chlorine analogs.

The direct iodination of nitroparaffins also proceeds readily in the presence of bases. Villiers (392) treated dinitromethane with iodine and potassium hy-droxide and obtained the monoiodo derivative in yellow crystals which rapidly decomposed. Seigle and Hass (353) found no difficulty in applying this reac-tion to mononitroparaffins, but the instability of the products renders them of little interest.

The foregoing discussion indicates that in the chlorination of nitroparaffins in the presence of bases the reaction is probably an addition to the nitronic acid or its salt, followed by loss of HX or MX.

$$R_2C{=}NO_2H + X_2 \longrightarrow R_2C{-}NO_2H \longrightarrow R_2CNO_2 + HX$$
$$\underset{X\ \ X}{|\ \ |} \qquad\qquad \underset{X}{|}$$
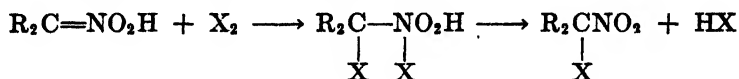
The reaction may also be viewed as an addition of a "positive" halogen atom to the anion of the nitronic acid with simultaneous formation of halide ion (403).

These mechanisms are in agreement with (1) the rapidity of the reaction, (2)

its occurrence in the absence of light, and (*3*) the fact that the halogen atom is always bound to the carbon atom which holds the nitro group.

2. Halogenation in the absence of bases

Riley and McBee (332) in this laboratory have investigated the action of chlorine and bromine upon nitroparaffins in the absence of bases and under the influence of phosphorus pentoxide and intense illumination. Bromine gives the same products as if a base were present. Chlorine, on the other hand, gives largely derivatives formed by substitution of hydrogen atoms other than those on the carbon atom holding the nitro group. Thus nitroethane yields almost exclusively 2-chloro-1-nitroethane, 1-nitropropane yields 2-chloro-1-nitropropane and 3-chloro-1-nitropropane, 2-nitropropane yields 1-chloro-2-nitropropane, nitrobutane yields the 2-, 3-, and 4-monochloro derivatives, and 1-nitro-2-methylpropane yields both the 2- and the 3-chloro derivatives.

In addition to the inherent interest in the reaction as a source of many bifunctional compounds not otherwise readily available, this work raises several theoretical questions, such as the following: Why do bromine and chlorine behave differently? Why does the presence of phosphorus pentoxide assist the reaction, while even a little water decreases the yield? We have already noted that acids (section X, B, 1) catalyze the nitronic acid–nitroparaffin tautomerization. If we imagine two competing reactions as follows, using nitroethane as an example,

$$CH_3CH_2NO_2 \xrightarrow[h\nu]{Cl_2} CH_2ClCH_2NO_2 + HCl$$

$$\downarrow H^+$$

$$CH_3CH{=}NO_2H \xrightarrow{Cl_2} CH_3CH{-}NO_2H \longrightarrow CH_3CHClNO_2 + HCl$$
$$\underset{Cl}{|} \underset{Cl}{|}$$
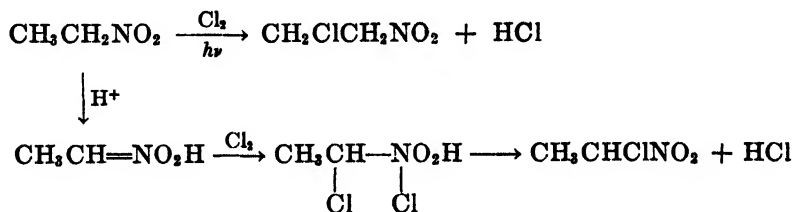
it is evident that water would, in the presence of hydrogen chloride, form hydrogen ions which favor the reëstablishment of the nitroparaffin–nitronic acid equilibrium after the chlorine had reacted with the trace of nitronic acid normally present. This would favor substitution on the alpha carbon atom. Phosphorus pentoxide hinders the addition reactions by preventing this. Bromine substitutes much more sluggishly than chlorine does, while it often adds to double bonds even more readily, so the nitronic acid mechanism is not so easily suppressed in this case

The effect of one or more chlorine atoms in decreasing the chlorination rate of the hydrogens upon a carbon atom (135) adjacent to the one holding the chlorine atom(s) seems analogous to the effect of the oxygen atoms here. It is interesting to note the close analogy between this reaction and the chlorination of monochloroacetone in the presence and absence of bases. In the presence of bases the reaction continues on the carbon atom holding the chlorine atom, since the hydrogen atoms in this position enolize more readily than those in the

methyl group. In the absence of bases and the presence of light the isomer is also formed (275).

E. CONDENSATION WITH ALDEHYDES TO YIELD NITROALCOHOLS

This reaction, discovered by L. Henry (146), is certainly the most versatile source of compounds derived from nitroparaffins. As an illustration we may use nitromethane and formaldehyde:

$$CH_3NO_2 + HCHO \xrightarrow[\text{of base}]{\text{trace}} HOCH_2CH_2NO_2 \xrightarrow{HCHO}$$

$$(HOCH_2)_2CHNO_2 \xrightarrow{HCHO} (HOCH_2)_3CNO_2$$
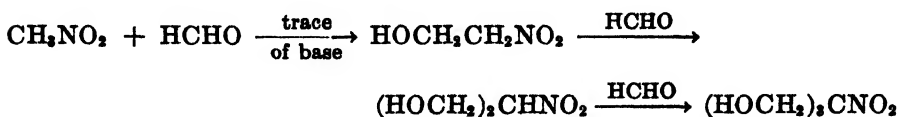
This is a condensation of the aldol type in which one, two, or three of the hydrogen atoms attached to the carbon atom holding the nitro group may add to the oxygen of an aldehyde with the formation of hydroxyalkyl-substituted nitroparaffins. The reaction almost certainly proceeds with the nitronic acids as intermediates. The function of the basic catalyst is to increase the concentration of aci-nitroparaffin by exerting its well-known catalytic effect in restoring the tautomeric equilibrium after the trace of nitronic acid normally present has reacted with aldehyde.

This mechanism is in harmony with the discovery of Kamlet (186) that an unusually rapid condensation between aldehydes and nitroparaffin can be obtained by using the sodium bisulfite addition compound of the aldehyde and the sodium salt of the aci-nitroparaffin. The function of the sodium bisulfite here is to liberate the nitronic acid from its salt without giving a sufficiently high concentration of hydrogen ions to destroy much of the nitronic acid *via* the Nef reaction discussed in section X, B, 2. A corollary is that other acid reagents should be capable of acting similarly, and this has been checked by Bourland (48) in this laboratory for carbonic acid, acetic acid, and sodium bisulfate. In some cases the use of carbonic acid increased the conversion appreciably over that obtainable with sodium bisulfite; in others the reverse was true.

A great variety of substances function successfully as the basic catalyst in this reaction; the list includes such diverse compounds as potassium and sodium hydroxides, carbonates, bicarbonates, and methoxides, and organic amines. Vanderbilt and Hass (390, 391) have pointed out the advantages of calcium hydroxide in view of its easy removal from the reaction mixture by conversion to insoluble salts.

In most cases the addition of aldehyde to nitroparaffin must compete with at least two other reactions: (*1*) the aldol condensation of the aldehyde with itself, and (*2*) the conversion of the nitroparaffin to an isoxazole or, in the case of nitromethane, to methazonic acid. It is therefore advisable to add as little catalyst as is necessary for a reasonably rapid reaction and to add the aldehyde gradually to the nitroparaffin so as to maintain its concentration at a low value and thus to suppress the formation of hydroxyaldehydes.

Both aldehydes and nitroparaffins vary tremendously in their ability to

undergo this reaction. Formaldehyde and nitromethane are both highly reactive and the rate decreases as either homologous series is ascended. Chloral reacts very rapidly, as would be expected from other behavior of its carbonyl group. With the homologs of nitromethane great difficulty is experienced in condensing more than a single aldehyde molecule on a nitroparaffin, unless one of the reagents is formaldehyde. Even with nitromethane the reaction often tends to stop with only one or two molecules of aldehyde condensed when the latter contains more than five carbon atoms. Secondary nitroparaffins react more sluggishly than primary ones and the tertiary isomers, having no alpha hydrogen atoms, do not react at all.

TABLE 4

Reaction of aldehydes with nitroparaffins

NITROPARAFFIN	MOLES ALDEHYDE	ALDEHYDE USED								
		Formaldehyde	Acetaldehyde	Propionaldehyde	n-Butyraldehyde	Isobutyraldehyde	Isovaleraldehyde	Benzaldehyde	Furfuraldehyde	Chloral or its hydrate
Nitromethane........	1	(118)	(156)	(181)	(181)	(345)	(362)	(334)	(187)	(69)
	2	(294)		(362)		(188)	(187)			
	3	(301)								
Nitroethane.........	1	(390)	(156)	(390)	(390)		(187)		(3)	(69)
	2	(390)								
1-Nitropropane	1	(390)	(390)	(390)	(390)		(187)			
	2	(390)								
2-Nitropropane	1	(390)	(390)	(390)	(390)					
1-Nitrobutane	1	(390)	(390)	(390)	(390)		(187)			
	2	(390)								
2-Nitrobutane	1	(390)	(390)	(390)	(390)					
1-Nitro-2-methyl-propane	1	(390)	(390)	(390)	(390)		(187)			
	2	(390)								
1-Nitropentane.......	1	(158)								
	2									
Nitroisopentane	1	(278)	(277)				(187)			
	2	(278)								
1-Nitrohexane	1	(158)								
	2									
Phenylnitromethane..	1	(168)						(195)		(69)

Traces of nitroölefins often are formed simultaneously with the nitroalcohols, and with aromatic aldehydes these may be the principal reaction products if amine catalysts are employed. Since many nitroölefins are prone to polymerize to form brown tars, they are objectionable impurities. Vanderbilt (389) has reported upon the removal of these compounds by polymerization, followed by distillation of the nitroalcohol.

Table 4 contains a summary of some of the nitroalcohols, nitroglycols, and "nitroglycerols" which have been produced from the simpler nitroparaffins and aldehydes. A "1" on the table means that one molecule of the aldehyde has been condensed, a "2" means two molecules, etc. The other numbers indicate the references.

The nitroalcohols available commercially, derived from nitroparaffins, are $(HOCH_2)_3CNO_2$, $(HOCH_2)_2C(CH_3)NO_2$, $HOCH_2C(CH_3)_2NO_2$, $(HOCH_2)_2C(C_2-H_5)NO_2$, and $CH_2OHCHNO_2C_2H_5$.

1. Derivatives of nitroalcohols

A detailed discussion of the many derivatives of the nitroalcohols would occupy too much space, but these compounds are so important that they deserve at least brief consideration.

The inorganic esters are represented by certain of the chloronitroparaffins previously discussed, which may be made by the chlorination of nitroparaffins or by the action of phosphorus pentachloride upon nitroalcohols. The nitrate esters may be produced from the nitroalkanols by the action of cold (0–20°C.), colorless, 100 per cent nitric acid in the presence of sulfuric acid.

$$(HOCH_2)_3CNO_2 + 3HNO_3 \xrightarrow{H_2SO_4} (O_2NOCH_2)_3CNO_2 + 3H_2O$$
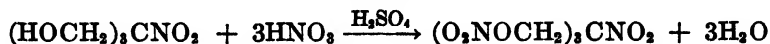
Hofwimmer (165) reported in 1912 concerning the product of this reaction that only the high cost of nitromethane stands in the way of its technological utilization. This compound is in perfect oxygen balance, has less sensitivity to shock than glycerol trinitrate, has 7 per cent more explosive power, and does not freeze under conditions ordinarily encountered. The dinitrate of 2-methyl-2-nitro-1,3-propanediol was patented in 1928 by Bergeim (26). It is also a high explosive.

The phosphate esters of the nitroalcohols and nitroglycols have been prepared by Vanderbilt, using phosphorus oxychloride (387), and have been studied as plasticizers for cellulose esters.

The esters of organic acids and nitroalcohols can be prepared by the use of acid anhydrides, acid chlorides, or, in some cases, the acids themselves in the presence of sulfuric acid and an agent, such as carbon tetrachloride, which removes water as a minimum azeotrope. Tindall (379) has recently reported ninety-six of these esters, all new compounds. They are of interest as plasticizers. While some are fairly stable at temperatures of 150°C., others are capable of being titrated at room temperature with standard alkali. This is due not to instantaneous saponification but to a reaction discovered by Schmidt and Rutz (346) which depends upon the presence of a hydrogen atom upon the carbon atom holding the nitro group.

$$
\begin{array}{c}
\overset{\displaystyle H \quad\;\; OCOCH_3}{\underset{\displaystyle NO_2 \;\; H}{R C \!-\!\!-\! C R}} \quad + \; NaHCO_3 \\[2em]
\qquad\qquad R\!-\!\underset{\displaystyle NO_2}{C}\!=\!CHR \; + \; CH_3COONa \; + \; H_2O \; + \; CO_2
\end{array}
$$
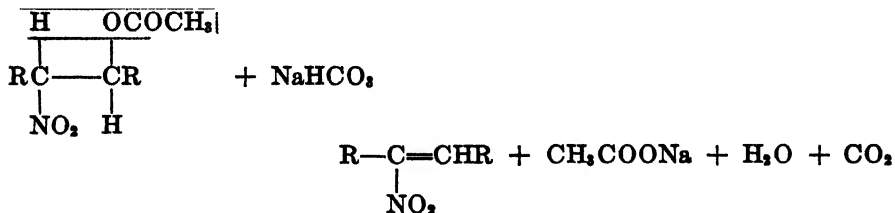
This reaction is of importance as the most general means of preparing nitro-olefins.

The production of resins of the glyptal type by condensing dibasic acids with 2-amino-2-methyl-1,3-propanediol has been reported (363).

Senkus has studied the formation of cyclic acetals by the condensation of aldehydes with polyhydric nitroalcohols. The reduction products of these compounds are aminocyclic acetals (354), some of which are "instantaneous wetting agents", so-called because in the Draves test (87) the yarn sinks at once in water containing 0.5 per cent of the acetal.

The reduction of nitroalcohols to aminoalcohols has been discussed in section X, A, 1. The ones derived from nitroparaffins commercially available at present are the following: $(HOCH_2)_3CNH_2$, $(HOCH_2)_2C(CH_3)NH_2$, $HOCH_2C(CH_3)_2NH_2$, $(HOCH_2)_2C(C_2H_5)NH_2$, and $CH_2OHCHNH_2C_2H_5$. With the higher fatty acids all of these compounds form soaps which are powerful emulsifying agents. With increased size and number of alkyl groups on the cation, they undergo a gradual transition from agents promoting emulsions of oil in water to those of the opposite type which cause water to disperse in oil. The principal applications of these compounds depend upon this emulsifying property, which is useful in the preparation of such diverse materials as cosmetics, pharmaceuticals, and floor waxes.

Many substances of pharmaceutical interest, such as ephedrine, $C_6H_5CHOH-CH(CH_3)NHCH_3$ and propadrine, $C_6H_5CHOHCH(NH_2)CH_3$, can readily be made by the aldehyde–nitroparaffin condensation followed by reduction and, if necessary, by alkylation and/or other known reactions. Even before nitroparaffins were readily available, these reactions were investigated and patented by W. N. Nagai (283) and Chogi Nagai (282). Fresh impetus to this field of research has resulted from the reduction of the price of nitroethane to less than 1 per cent of its former figure.

F. CONDENSATION WITH ALDEHYDES TO YIELD NITROÖLEFINS

Although inorganic bases cause aromatic aldehydes to react with nitroparaffins, yielding nitroalcohols, these reagents in the presence of amines yield nitroölefins. This reaction may be formulated as follows:

$$ArCHO + RNH_2 \rightarrow ArCH{=}NR + H_2O$$

$$ArCH{=}NR + RCH_2NO_2 \rightarrow RNH_2 + ArCH{=}C(NO_2)R$$
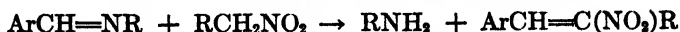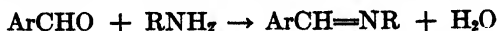
By the term "aromatic aldehydes" is meant only compounds in which the aldehyde group is attached directly to a nucleus capable of resonance; phenylacetaldehyde would not be included, while furfuraldehyde would be. The difference between the behavior of the two classes of aldehydes is only one of degree, since nitroölefins are always formed to some extent when an aldehyde reacts with a nitroparaffin, and is presumably attributable to the ease of dehydration of the nitroalcohol which contains an hydroxyl group in a position alpha to an aromatic nucleus.

ω-Nitrostyrene is so easily prepared from benzaldehyde and nitromethane (410) that it has been rather widely studied. Although Simon (359) had made this compound from styrene long before, the first preparation by this condensation was made by Priebs (315), who in 1884 used zinc chloride as the cata-

lyst.   Posner in 1898 (312) confirmed and extended this work, but the next year Thiele (376) reported much better results, using alcoholic potassium hydroxide followed by acidification with hydrochloric acid.   Except for the substitution of sodium hydroxide for the potassium analog, this is still the preferred procedure.   Bouveault and Wahl (50) used sodium methoxide in place of potassium hydroxide, but since the alkali metal salt of nitromethane is formed in either

TABLE 5

Nitrostyrene and related compounds

	MELTING POINT OR BOILING POINT*
	°C.
ω-Nitrostyrene	58 (317, 376); 57 (195)
1-Phenyl-2-nitropropene	64 (317); 64 (195); 65 (3)
1-Phenyl-2-nitro-1-butene	125–129 at 10 mm. (372)
ω,o-Dinitrostyrene	107 (50, 312)
ω,m-Dinitrostyrene	122–124 (312); 125 (376)
ω,p-Dinitrostyrene	196–199 (376)
p-Methoxy-ω-nitrostyrene (anisylidenenitromethane)	87 (50); 86 (195)
3,4-Methylenedioxy-ω-nitrostyrene	159 (50); 158 (195); 161.5 (220)
2,4-Dimethoxy-ω-nitrostyrene	104 (322)
3,4,5-Trimethoxy-ω-nitrostyrene	120–121 (360); 119–120 (250)
2,3,4-Trimethoxy-ω-nitrostyrene	167 (360)
p-Hydroxy-ω-nitrostyrene	154–160 (334)
3,4-Dihydroxy-ω-nitrostyrene	155–157 (334)
2-Hydroxy-4-methoxy-ω-nitrostyrene	171–172 (322)
2-Ethoxy-4-methoxy-ω-nitrostyrene	102 (322)
1-Piperonylidene-1-nitroethane	98 (195)
1-Anisylidene-1-nitroethane	48 (195); 43–44 (3)
3-Methoxy-4-hydroxy-ω-nitrostyrene	165 (195); 160–164 (334)
1-(3,4-Dimethoxybenzylidene)-1-nitroethane	70–71 (3)
1-Furyl-2-nitroethene	74 (50)
1,4-Bis(β-nitrovinyl)benzene	200–230 (376, 412)
1-Furyl-2-nitrobutylene	130–131 at 13 mm. (187)
1-Furyl-3-methyl-2-nitrobutylene	122–123 at 13 mm. (187)
1-Furyl-2-nitroamylene	136–137 at 13 mm. (187)
Vanillylidenenitromethane benzyl ether	122–123 (220)
Anisylidenenitroethane	48 (195)
5-ω-Dinitro-2,4-dimethoxystyrene	214 (322)
1,4-Bis(β-methyl-β-nitrovinyl)benzene	119–120 (412)
1,4-Bis(β-nitro-β-phenylvinyl)benzene	228–229 (decompn.) (412)

* References to the literature are given in parentheses.

case, it seems unlikely that the results would justify the use of the more expensive reagent.

Thiele found that when the alkali salt is acidified with a mineral acid, nitrostyrene results but that acetic acid yields the corresponding nitroalcohol.

$$C_6H_5CHOHCH{=}NO_2K + HCl \rightarrow C_6H_5CH{=}CHNO_2 + H_2O$$

$$C_6H_5CHOHCH{=}NO_2K + CH_3COOH \rightarrow C_6H_5CHOHCH_2NO_2 + CH_3COOK$$
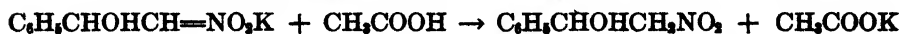
This result was corroborated by Holleman (168) and also by Rosenmund (334).

The aromatic nitroölefins listed in table 5 have been synthesized.

1. *Other syntheses of nitroölefins*

In 1928 Schmidt and Rutz (347) reported that acetic acid could be abstracted from certain acetates of nitroalcohols by refluxing the esters in ether solution with potassium carbonate or bicarbonate. Nitroölefins are thus produced in good yields. As modified in this laboratory by A. G. Susie (372), this synthesis is represented by the following equation:
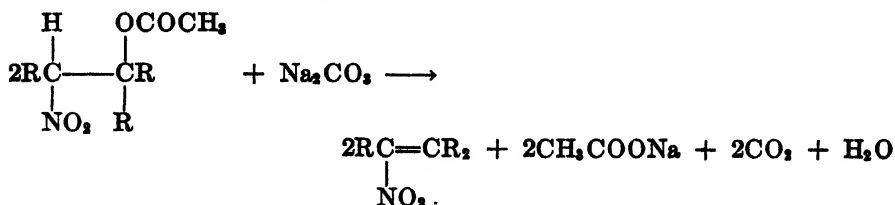
$$2RC\overset{\underset{\displaystyle NO_2}{|}}{\underset{}{\overset{\displaystyle H}{|}}}{-}CR\overset{\underset{\displaystyle R}{|}}{\overset{\displaystyle OCOCH_3}{|}} + Na_2CO_3 \longrightarrow$$

$$2RC{=}CR_2 + 2CH_3COONa + 2CO_2 + H_2O$$
$$\underset{NO_2}{|}$$

Since nitroparaffins and aldehydes readily yield nitroalcohols, which in turn are easily acylated, the nitroölefins are thus readily accessible. Benzene proved to give better yields than ether when used as a solvent in this reaction. It should be pointed out that only the isomers having nitro groups on the doubly bound carbon atoms can thus be made. Naturally, in the nitroalcohol the carbon atom holding the nitro group must also be attached to a hydrogen atom.

Other means of producing nitroölefins include the nitration of tertiary alcohols (121, 122). The abstraction of HX from a halonitro compound has been used to produce nitro compounds of the acetylene series (230). The action of dehydrating agents upon nitroalcohols (405, 407), the reaction of silver nitrite upon allylic halides, and the cautious decomposition of nitronitrates (407) are also applicable.

$$(CH_3)_3COH + HNO_3 \longrightarrow (CH_3)_2C{=}CHNO_2 \quad (121)$$

$$(CH_3)_2(C_2H_5)COH + HNO_3 \longrightarrow CH_3C\overset{\overset{\displaystyle CH_3}{|}}{=}C\overset{\overset{\displaystyle NO_2}{|}}{}CH_3 \quad (123)$$

$$HOCH_2CH_2NO_2 \xrightarrow{NaHSO_4} CH_2{=}CHNO_2 + H_2O \quad (405)$$

$$CH_2{=}CHCH_2Br + AgNO_2 \longrightarrow CH_2{=}CHCH_2NO_2 + AgBr^{13}$$

$$ClCH(NO_2)CH_2NO_2 \xrightarrow{heat} CH_2{=}CClNO_2 + HNO_3 \quad (407)$$
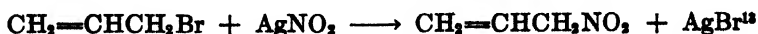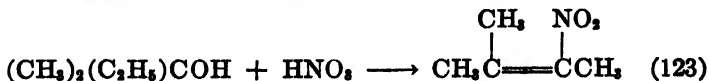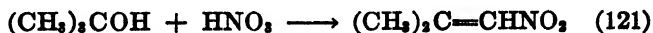
Because of the ease of addition of halogens to nitroölefins, these reactions lead readily to polyhalonitro compounds.

Hydroxysubstituted nitroölefins may be produced by condensing unsaturated aldehydes with nitroparaffins (362):

$$CH_3CH{=}CHCHO + CH_3NO_2 \rightarrow CH_3CH{=}CHCHOHCH_2NO_2$$
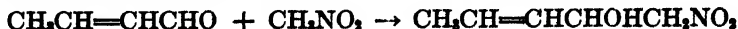
[13] Brackebush (56) first reported this reaction, but his work was attacked and discredited by R. Schiff (342), who showed that he had not prepared a new nitroölefin but in reality the substance he reported as boiling at 96°C. was mostly water. Later Meyer and Askenasy (260) made this nitroölefin from allyl iodide, while Henry (152) prepared it from allyl bromide and silver nitrite.

2. *Reduction of nitroölefins to amines*

If the nitroölefins produced as described in the foregoing section can be reduced completely, these reactions indicate methods of preparing amines of definite structures free from isomers. This problem has received considerable attention.

Alles (3) attempted to produce benzedrine (α-methylphenethylamine) by the reduction of the corresponding nitroölefin. He reports that "the complete reduction of 1-phenyl-2-nitro-1-propene involves considerable difficulty, . . . and several attempts at catalytic hydrogenation or reduction with various metals or their amalgams were not at all successful." His best yield (20 per cent) was obtained electrolytically, using a mercury cathode and a catholyte comprising ethanol, acetic acid, and sulfuric acid. Employment of the more recently developed Raney nickel catalyst enables one to obtain about a 40 per cent yield in this same reduction (380).
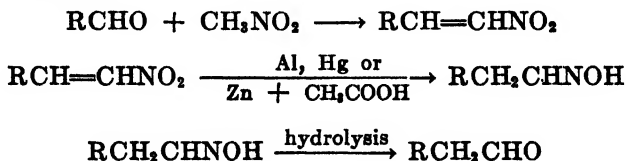
Schales (339) converted ω-nitrostyrene to β-phenethylamine in 93 per cent yield by using the platinum oxide catalyst of Adams and Shriner and adding the nitrostyrene gradually to the hydrogenation vessel. A mixture of acetic and sulfuric acids was used as solvent. Similar results were obtained with 3,4-methylenedioxy-ω-nitrostyrene and 3-nitro-ω-nitrostyrene, both nitro groups being reduced to amino groups in the latter compound.

Reichert and Koch (326, 327) reduced the nitroölefins obtained by condensing nitromethane with the following aldehydes: o-methoxybenzaldehyde, anisaldehyde, veratric aldehyde, and piperonal. By the use of palladium on animal charcoal almost quantitative yields of the oximes are obtained. These can then be converted to the amines by using a platinum catalyst.

3. *Reduction of nitroölefins to aldoximes, ketoximes, and ketones*

O. Wallach (394) reported the reduction of 1-anisyl-2-nitropropene to 1-anisyl-2-propanone oxime and of 1-piperonyl-2-nitropropene to 1-piperonyl-2-propanone oxime by the use of zinc and acetic acid at 0°C. Bouveault and Wahl (51, 52) reported that homologous series could be ascended by the following sequence of reactions:

$$RCHO + CH_3NO_2 \longrightarrow RCH{=}CHNO_2$$

$$RCH{=}CHNO_2 \xrightarrow[\text{Zn + CH}_3\text{COOH}]{\text{Al, Hg or}} RCH_2CHNOH$$

$$RCH_2CHNOH \xrightarrow{\text{hydrolysis}} RCH_2CHO$$

Subsequent workers have been unable to repeat the work of Bouveault and Wahl.

A. G. Susie (372) in this laboratory found that iron turnings and hydrochloric acid effect the reduction of nitroölefins to mixtures of the corresponding ketones and ketoximes in yields of about 70 per cent. The reaction may be controlled to yield almost exclusively ketone when sufficient hydrochloric acid is employed and almost exclusively ketoxime when a minimal quantity of acid is present.

This work has been confirmed and extended by R. L. Heider (142). Since either the ketoxime or the ketone (in the presence of ammonia) may be reduced to the corresponding amine by the use of Raney nickel and hydrogen, this constitutes an inexpensive and efficient two-step conversion of nitroölefins to amines. So far, the reaction has been successful in every instance where tried. Table 6 gives a list of the nitroölefins reduced and the ketones obtained.

TABLE 6

Reduction of nitroölefins to ketones

NITROÖLEFIN	KETONE
3-Nitro-2-pentene......................................	3-Pentanone
2-Nitro-2-hexene.......................................	2-Hexanone
4-Nitro-4-octene.......................................	4-Octanone
1-Phenyl-2-nitropropene...............................	Phenylacetone
1-Phenyl-2-nitrobutene................................	1-Phenyl-2-butanone
1-Phenyl-2-nitropentene..	1-Phenyl-2-pentanone
1-Furyl-2-nitropropene	Furylacetone
1-Anisyl-2-nitrobutene......................... ..	1-Anisyl-2-butanone
1-Anisyl-2-nitropentene...............................	1-Anisyl-2-pentanone

4. Addition of nitroölefins to cyclopentadiene

Since nitroölefins,
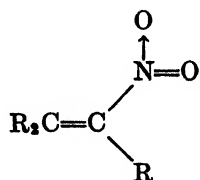
contain an activated double bond, it seems that they should be suitable reagents for the Diels–Alder reaction. This has been reported in an article by Alder, Rickert, and Windemuth (2). Nitroethylene, 1-nitropropene, and 1-nitro-1-pentene were each treated with cyclopentadiene and the expected products were obtained. 1-Nitro-1-pentene was also added to butadiene, methylbutadiene, and 2,3-dimethylbutadiene.
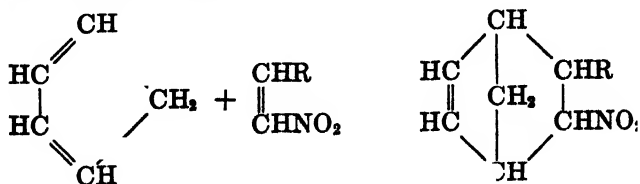
The nitroölefins were reduced to the saturated amines. It is evident that here is a fertile field for research.

5. Addition of nitroölefins to compounds containing active hydrogen

It is perhaps premature to state that all or most compounds with active hydrogen add to nitroölefins, but the evidence so far points in that direction.

$$R_2C{=}C(NO_2)R' + HA \longrightarrow R_2C{-}C(NO_2)R'$$
$$\underset{A}{|} \quad \underset{H}{|}$$
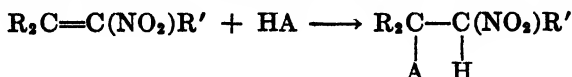
Either the concept of 1,4-addition or that of relative electronegativity would predict the direction of this reaction. The addition of phenylnitromethane to diphenylnitroethylene and the formation of dinitroneopentane from 1-nitro-2-methylpropene and nitromethane have been mentioned in section VI. This reaction is receiving further study as a means of obtaining dinitroparaffins.

Nitroölefins are readily hydrolyzed by the action of dilute sulfuric acid, as follows (372):

$$RCH{=}C(NO_2)R' + H_2O \xrightarrow{H_2SO_4} RCHOHCHNO_2R'$$

$$RCHOHCHNO_2R' \longrightarrow RCHO + R'CH_2NO_2$$

$$R'CH_2NO_2 + H_2O + H_2SO_4 \longrightarrow R'COOH + NH_2OHHSO_4$$
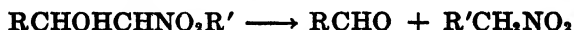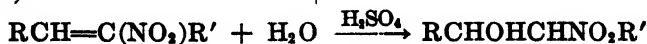
Askenasy and Meyer (10) had previously reported small amounts of acrylic acid from the hydrolysis of 1-nitropropene. In the first step of this reaction water functions as the compound containing active hydrogen.

P. Friedlander and J. Mähly (104) reported that treatment of p-nitro-ω-nitrostyrene with alcoholic potassium hydroxide dissolved it with the formation of $O_2NC_6H_4CH(OC_2H_5)CHNO_2K$.

Meisenheimer and Heim (253, 254) and Rosenmund (334) reported that ω-nitrostyrene adds sodium methoxide or ethoxide instantaneously, as follows:

$$C_6H_5CH{=}CHNO_2 + NaOCH_3 \rightarrow C_6H_5CH(OCH_3)CH{=}NO_2Na$$
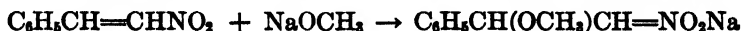
The resulting solution is instable and yields $C_6H_5CH(OCH_3)CHNO_2CH(C_6H_5)$-$CH_2NO_2$.

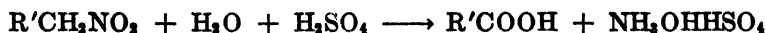Reichert and Koch (327) used this reaction to prepare α-(2-methoxyphenyl)-β-nitroethyl methyl ether, α-(4-methoxyphenyl)-β-nitroethyl methyl ether, and α-(3,4-dimethoxyphenyl)-β-nitroethyl methyl ether.

The addition of acetone to 1-nitro-2-methylpropene yields 5-nitro-4,4-dimethyl-2-pentanone (48).

$$CH_3COCH_3 + (CH_3)_2C{=}CHNO_2 \longrightarrow O_2NCH_2\overset{\overset{\displaystyle CH_3}{|}}{\underset{\underset{\displaystyle CH_3}{|}}{C}}CH_2COCH_3$$
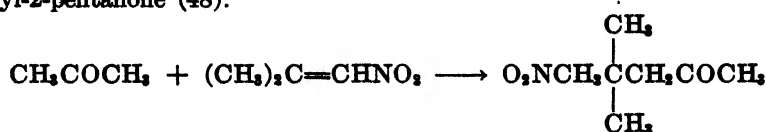
An interesting addition reaction which might be mentioned in this connection is that postulated by Holleman (167) to explain the changes observed when ω-nitrostyrene was treated with potassium cyanide and then acidified. Before the formation of a bimolecular condensation product he postulated the reaction:

$$C_6H_5CH{=}CHNO_2 + KCN \rightarrow C_6H_5CH(CN)CH{=}NOOK$$
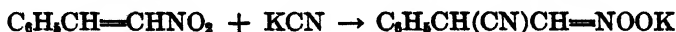
Upon acidification, hydrocyanic acid splits out between two molecules and a bimolecular product results.

The action of amines or ammonia on 1-bromo-1-nitro-1-butene and on 1-bromo-1-nitro-1-pentene yields the corresponding amine derivative (231) in each case.

G. REACTION OF ARYLDIAZONIUM SALTS WITH SALTS OF ACI-NITROPARAFFINS

This condensation was discovered by Victor Meyer and Ambühl (259), who mixed aqueous solutions of benzenediazonium sulfate and sodium nitroethane and obtained an orange solid, which they formulated as $C_6H_5N=NCH(NO_2)CH_3$ and which possessed the definitely acidic properties to be expected of such a compound. The fact that two equivalents of metal were present in the salts was entirely unanticipated, since the formula indicates only one replaceable hydrogen atom. The corresponding compound was therefore made from 2-nitropropane and when this proved to have no acidic properties the metallic derivatives of phenyldiazo-1-nitroethane were formulated as basic salts, e.g.,

$$C_6H_5N=N\overset{\overset{\displaystyle NO_2}{|}}{\underset{\underset{\displaystyle ZnOH}{|}}{C}}CH_3 \cdot 2H_2O$$
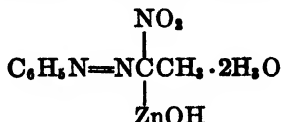
The same year Friese, working in Meyer's laboratory, reported the condensation of benzenediazonium nitrate with sodium nitromethane to yield phenyldiazonitromethane (105), a red solid giving a blue-violet solution in sulfuric acid, from which it can be recovered unchanged by diluting with water. His results were later shown to be incorrect, however, the compound obtained from nitromethane being formulated by Bamberger (12) as N,N'-diphenyl-C-nitroformazyl, $C_6H_5N=NC(NO_2)=NNHC_6H_5$.

In rapid succession the following compounds were reported: 1-phenyldiazo-1-nitropropane; 1-(p-tolyldiazo)-1-nitroethane; 1-(o-tolyldiazo)-1-nitroethane; 1-(p-bromophenyldiazo)-1-nitroethane; and 1-(m-nitrophenyldiazo)-1-nitroethane (269).

Askenasy and Meyer (10) obtained 3-nitropropene—after previous efforts over twenty years had been unsuccessful—and caused it to react with benzenediazonium sulfate, p-toluenediazonium sulfate, o-toluenediazonium sulfate, p-anisolediazonium sulfate, p-phenetolediazonium sulfate, m-carboxybenzenediazonium sulfate, m-bromobenzenediazonium sulfate, p-chlorobenzenediazonium sulfate, and pseudocumenediazonium sulfate; in each case they obtained the expected compound.

When Keppler and Meyer prepared 1,3-dinitropropane (191) they condensed it with 2 moles of benzenediazonium sulfate, and also made the corresponding derivatives of p-toluidine and p-methoxyaniline. Many other compounds have been similarly prepared by Bamberger et al. (14, 15, 16), Chattaway, Drewitt, and Parkes (68), Hantzsch and Kissel (124), Jones and Kenner (181), and Ponzio and students (308, 309, 310). Feasley, working in this laboratory, has synthesized a large number of diazo derivatives of 2-nitropropane and 2-nitrobutane.

H. ADDITION OF NITROPARAFFINS TO ACTIVATED DOUBLE BONDS

The addition of nitroparaffins to nitroölefins has already been mentioned in sections VI and X, F, 5.

The addition of nitroparaffins to unsaturated ketones was first reported by Kohler (196), who found that primary or secondary nitroparaffins in the presence of various bases add to α,β-unsaturated ketones, esters, nitriles, and nitro compounds. Organic bases such as diethylamine or piperidine are recommended as catalysts for the addition to methyl ketones, such as benzalacetone, while sodium ethoxide gives better results with benzalacetophenone. "A small quantity of sodium alcoholate is sufficient to cause rapid disappearance of both ketone and nitro compound; but under these conditions the result is always a mixture of complex products."

$$C_6H_5CH{=}CHCOC_6H_5 \;+\; CH_2{=}NO_2Na \longrightarrow C_6H_5CHCH_2COC_6H_5$$

$$\underset{\displaystyle CH{=}NO_2Na}{|}$$

$$\downarrow HCl$$

$$C_6H_5CHCH_2COC_6H_5$$
$$\underset{\displaystyle CH_2NO_2}{|}$$

$$C_6H_5CH{=}CHCOC_6H_5\nearrow$$

$$C_6H_5CHCH_2COC_6H_5$$
$$\underset{\displaystyle C{=}NO_2Na}{|}$$
$$C_6H_5CHCH_2COC_6H_5$$

"These are due to the fact that the sodium compound formed from one molecule each of ketone and sodium nitromethane readily combines with more of the unsaturated ketone ... therefore it is necessary to have an excess of sodium nitromethane *in solution*."

Table 7 contains a summary of the work of Kohler and students.

I. ANALYTICAL REACTIONS OF NITROPARAFFINS

Early students of the nitroparaffins frequently utilized combustion analyses for the determination of carbon, hydrogen, and nitrogen. Meyer, Henry, Worstall, Konovalov, and other investigators who carried out many such experiments gave analytical data of this kind and, in addition, gave the results of vapor-density determinations carried out by Hoffman's method. While the results of combustion analyses are valid when the work is carefully done, they present difficulties when the compound is especially volatile or when it tends to burn too readily. While the nitroparaffins *per se* are not particularly explosive, some compounds derived from them are explosible under such conditions.

Almström (4) was aware of this difficulty and gave a modification of Pregl's method of microanalysis adapted for use when the compound showed these undesirable characteristics. He mixed the sample with washed and ignited sand, which modified the burning so that it proceeded quietly and the analysis

TABLE 7

Compounds prepared from nitroparaffins by Kohler and students

COMPOUND REACTED	PRODUCT FORMED FROM NITROMETHANE*	PRODUCT FORMED FROM NITROETHANE	PRODUCT FORMED FROM 2-NITROPROPANE
$C_6H_5CH=CHCOCH_3$	$C_6H_5CHCH_2COCH_3$ (196) CH_2NO_2	$C_6H_5CHCH_2COCH_3$ (196) CH_3CHNO_2	$C_6H_5CHCH_2COCH_3$ (196) $(CH_3)_2CNO_2$
$C_6H_5CH=C(COOCH_3)_2$	$C_6H_5CHCH(COOCH_3)_2$ (198) CH_2NO_2		
$C_6H_5CH=CHCH=C(COOCH_3)_2$..	$C_6H_5CH=CHCHCH(COOCH_3)_2$ (198) CH_2NO_2		
$C_6H_5COCH=CHCOOCH_3$	$C_6H_5COCH_2CHCOOCH_3$ (198) CH_2NO_2		
$C_6H_5CH=CHCOC(CH_3)_3$	$C_6H_5CHCH_2COC(CH_3)_3$ (199) CH_2NO_2		
$C_6H_5CH=CHCO$⟨benzene⟩Cl ...	$C_6H_5CHCH_2CO$⟨benzene⟩Cl (200) CH_2NO_2		
Cl⟨benzene⟩CH=CHCOC₆H₅	Cl⟨benzene⟩CHCH₂COC₆H₅ (200) CH_2NO_2 CH_3		
$(CH_3)_2C=CHCOCH_3$	$CH_3CCH_2COCH_3(?)$† (196) CH_2NO_2		

* References to the literature are given in parentheses.

† The reason for the question mark opposite the formula of mesityl oxide is that, although Kohler states, in discussing the use of organic amines as catalysts, "In the case of . . mesityl oxide this is the best procedure," he apparently never reported the expected compound. Inquiry by the authors since Professor Kohler's demise has been unavailing.

gave dependable results. When salts of the alkali metals were analyzed, lead chromate was used instead of sand in order to prevent the formation of a residue of alkali carbonate.

Friedemann (103) suggested an analysis based on oxidation by chromic acid. In this method a 0.1-g. sample is dissolved in concentrated sulfuric acid and 0.2 N potassium dichromate solution is added. The material is oxidized by boiling gently under reflux, then potassium iodide is added, and the mixture is titrated with sodium thiosulfate. More sulfuric acid is required for difficultly combustible compounds; sugar requires about 2 ml., trinitrotoluene about 10 ml. An accuracy of 0.0001 to 0.001 g. is claimed for this method.

Other procedures for analysis have been modified in a manner which permits their application to the nitroparaffins. The unmodified Kjeldahl method for nitrogen determination is not satisfactory for such compounds, because most nitroparaffins and their derivatives are difficult to digest to colorless solutions by the use of sulfuric acid alone. Their high volatility makes an unduly prolonged process untenable. Šimek (358) proposed a modified method, and Harte (130) devised a method of shortening the digestion period by using dextrose, potassium sulfate, copper sulfate, and alundum and digesting the sample in sulfuric acid.

A different means of attacking the problem of analysis of nitroparaffins is offered by Kirpal (192), Limpricht (226), and Mulliken and Barker (279), who describe a quantitative method based on reduction of the nitro group. In all the examples given in Limpricht's paper aromatic nitro compounds were employed, but Mulliken and Barker (279) and Kirpal (192) reduced nitroparaffins as well. Wallerius (395) showed that the nitrogen content of aliphatic or aromatic nitro compounds can be determined by reducing them with stannous chloride and subsequently titrating with iodine. Ponzio (306) reported that this method is not applicable to dinitroparaffins, since they sometimes have only one nitro group which is capable of reacting with stannous chloride.

Oldham (288) has given a titration method designed to determine the number of nitro groups in a compound. Hearon and Gustavson (141) proposed a semimicro qualitative test for the detection of nitroparaffins, and Priebs (315) suggested that the reaction between benzaldehyde and nitromethane to yield nitrostyrene could be made a quantitative test for nitromethane.

Colorimetric methods of analysis have been widely tested with a view to developing more rapid means of determining nitroparaffins. Meyer, whose tests to distinguish primary, secondary, and tertiary nitroparaffins have already been discussed (section X, B, 3), was one of the first to use such methods. Konovalov (207, 208) studied the bright red color produced by ferric chloride in benzene solutions of primary nitroparaffins in the presence of alcoholic potassium hydroxide and reported that 5 ml. of a solution of 1-phenyl-1-nitropropane containing 1 part in 1400 parts of benzene gave a distinct red color after 1 hr. This method was suggested by Konovalov for use with nitroparaffins of more than six carbon atoms, which do not react very satisfactorily when treated with nitrous acid by Meyer's method.

Bose (46) pointed out the disadvantage that Meyer's method possesses, i.e., it gives no reaction with tertiary nitro groups. He also noted that the Kjeldahl and other quantitative methods for nitrogen determination provide no means of distinguishing various types of nitrogen-containing groups. He proposed instead a colorimetric method based on the Greiss-Ilosvay sulfanilic acid reagent. The nitro compound is heated with potassium hydroxide solution, the mixture is cooled, water is added, and the alkaline solution is acidified with acetic acid and then treated with the Greiss-Ilosvay reagent[14]; a red color develops in the presence of a nitro group. Only a few of the many compounds investigated failed to respond to this test, and the list of inert compounds included no nitroparaffins.

Bost and Nicholson (47) give color tests for the identification of mono- and tri-nitro compounds which seem, however, more applicable to members of the aromatic series.

Scott, Treon, and other investigators at the Kettering Laboratory of Applied Physiology have developed colorimetric analyses for nitroparaffins. They have found it possible to use several reactions, such as that with ferric chloride, which produces a red color in the presence of acid. The color is believed to depend on the presence of aci-nitroparaffin. Absorption curves in the visible range show maxima at 500 mμ. At this wave length they follow Beer's law in the concentrations used. Data obtained by the analysis of air samples were presented (351). Machle, Scott, and Treon (241), in the work on the analysis of air-nitroparaffin mixtures, found that samples containing high concentrations of mononitroparaffins could be aspirated through a 50-cm. interferometer, but this method was not sufficiently sensitive for air containing lower concentrations, and chemical detection was therefore necessary. The samples were taken in evacuated bulbs in which the nitroparaffin was dissolved in alkali. The method was based on the color formed by heating nitromethane and vanillin in ammoniacal solution. This color does not follow Beer's law, so two known concentrations of nitromethane, one greater and one less than that of the unknown, must be determined at the same time.

These investigators also developed a color test for 1,1-dichloro-1-nitroethane. The dichloronitroparaffin is dissolved in methanol and treated with a 5 per cent solution of resorcinol in methanol, 5 per cent aqueous sodium hydroxide is added, and water is put in; after the solution has stood in an ice chest for 4 hr. a green color develops which becomes light yellow on acidification. The color is read against a water blank in 1-in. matched cells at 480 mμ on a spectrophotometer. From a previously prepared standardization curve, after subtraction of the blank, the result is read as milligrams of 1,1-dichloro-1-nitroethane. The standardization curve must be rechecked each time a new batch of alcohol is used. The blank is determined each time and is consistently low.

Manzoff (243) had previously developed a test based on the color resulting from the reaction of nitromethane with vanillin in the presence of ammonia.

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[14] Sulfanilic acid (0.5 g.) plus 150 ml. of 2 N acetic acid is mixed with a colorless solution prepared by adding 0.1 g. of pure α-naphthylamine to 20 ml. of boiling water.

He proposed it as a test for methanol in ethanol, since a mixture of the alcohols, converted to nitromethane and nitroethane *via* the Victor Meyer reaction, gives a red color, while nitroethane when similarly treated gives only a pale yellow color.

Desvergnes (84) described a colorimetric method for determination of nitroparaffins, which utilizes the reaction with bases to produce a yellow color. Since the color thus produced seems to vary somewhat with the temperature of reaction, high accuracy would not be predicted for this method unless the temperature were carefully controlled.

Ivett (174), using the dropping-mercury electrode, determined the half-wave potentials of six aliphatic nitro compounds in solutions containing an excess of sulfuric acid or sodium sulfate, and the possibility of determining these compounds quantitatively was investigated. The compounds were found to be reduced at a lower potential in acid than in neutral solutions. The ease of reduction increases with increasing molecular weight and is greater for secondary than for primary nitro compounds. The current flow was found to be proportional to the concentrations of nitroparaffins in acid solutions, but in the neutral solutions there were slight but reproducible deviations from this linear relationship.

Numerous analyses designed to determine chloropicrin and other halonitroparaffins appear in the literature (88, 97), and numerous stability tests usually applied to explosives (for example, the well-known Abel test (1)) have been extended to some of the nitroparaffins.

Macbeth and Pratt (240) have shown that in the case of most halogen-substituted nitromethanes the halogen is labile. Chlorotrinitromethane is reduced quantitatively according to the equation:

$$2CCl(NO_2)_3 + 4KOH + N_2H_4 \rightarrow 2CK(NO_2)_3 + N_2 + 4H_2O + 2KCl$$

This reaction may be used to estimate the amounts of different nitro compounds in a mixture.

Polynitroparaffins as analytical reagents

Because of their tendency to react with unsaturated compounds with the production of characteristic colors, many polynitro- or halonitro-paraffins have been employed as analytical reagents. Papers noting this means of characterizing the colored materials are too numerous to summarize but are listed with the compounds which may be so tested.

Harper and Macbeth (128) believe the colors are due to intermediate addition products and that the final products are colorless.

Clarke, Macbeth, and Steward (74) investigated a number of reactants, both organic and inorganic, and found that reagents prepared from polynitroparaffins give characteristic colors with compounds containing elements capable of showing valence changes.

Mononitroparaffins find other uses in analysis. Mulliken and Wakeman (280, 281) proposed the use of nitromethane as a group reagent in qualitative

organic analysis. Alkanes, cycloalkanes, dicycloalkanes, alkenes (usually), cycloalkenes, and alkadienes containing eight or more carbon atoms are immiscible with nitromethane at 20°C. Aromatic compounds are much more soluble. The presence of an aromatic ring is indicated if an unknown hydrocarbon boiling in the ranges 100–220°C. and 220–300°C. shows miscibility at 20°C. and 55°C., respectively, with nitromethane.

TABLE 8

*Color tests using polynitroparaffins**

REAGENT	REACTANTS	INVESTIGATORS
Tetranitromethane............	S⁻ ⁻	Harper and Macbeth (127)
Tetranitromethane............	—NH₂ compounds	Harper and Macbeth (127)
Tetranitromethane............	C=C	Harper and Macbeth (127)
Tetranitromethane............	Unsaturated compounds	Hurd and Bollman (172)
Dibromodinitromethane......	Unsaturated compounds	Hurd and Bollman (172)
Nitroform...................	Unsaturated compounds	Hurd and Bollman (172)
Tetranitromethane............	Unsaturated compounds	Werner (400)
Tetranitromethane..........	Amines of androsterone series, etc.	Ruzicka (336)
Tetranitromethane.......	Unsaturated compounds	Ostromisslensky (293)
Dibromodinitromethane......	Unsaturated compounds	Ostromisslensky (293)
Nitroform..........	Unsaturated compounds	Ostromisslensky (293)
Alkyl nitrites.................	S⁻ ⁻, C=C, —NH₂	Harper and Macbeth (128)
Tetranitromethane............	Unsaturated compounds	Harper and Macbeth (129)
Substituted nitreforms........	Unsaturated compounds	Graham and Macbeth (119)
Tetranitromethane............	Sterols and aminosterols	Butenandt and Tscherning (62)
Tetranitromethane............	Unsaturated compounds	Will (408)

* Other papers along similar lines are those of references 72, 116, 117, 176, 290, 328, 337, 371, 396. The list is not exhaustive.

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